IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 07-731
IMPAX LABORATORIES, INC.,	)	
Defendant.	)	

PLAINTIFFS' OPENING BRIEF IN SUPPORT OF MOTION FOR EXPEDITED DECLARATORY JUDGMENT RELIEF

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld (#1014)
Mary B. Graham (#2256)
Julia Heaney (#3052)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
jblumenfeld@mnat.com
mgraham@mnat.com
jheaney@mnat.com
Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

Of Counsel:

Martin J. Black
George G. Gordon
Ann M. Caviani Pease
Robert D. Rhoad
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
(215) 994-4000

Robert J. Gunther, Jr.
Lisa J. Pirozzolo
James P. Barabas
WILMER CUTLER PICKERING HALE AND DORR LLP
399 Park Avenue
New York, NY 10022
(212) 230-8800

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NATURE AND STAGE OF PROCEEDING

Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest") (collectively, "Plaintiffs") filed this action against defendant Impax Laboratories, Inc. ("Impax") on November 15, 2007. Pursuant to Fed. R. Civ. P. 57, Plaintiffs now move for expedited declaratory judgment relief, declaring that Impax's attempt to trigger the process for resolving patent disputes relating to Abbreviated New Drug Applications ("ANDAs") was premature, improper and contrary to law. Resolving Plaintiffs' request for declaratory judgment relief requires no discovery. Nor does it require an evidentiary hearing. Rather, it raises a pure legal issue that turns on a simple and undisputed fact: as Impax has admitted, the FDA has rescinded acceptance of its ANDA for a generic version of OPANA® ER. Because Impax has no ANDA which has been accepted for substantive review, Impax's attempt to trigger the ANDA patent dispute resolution process is null and void as a matter of law.

SUMMARY OF ARGUMENT

In the so-called "Hatch-Waxman Act," Pub. L. No. 98-417, *codified at* 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271, 282, Congress crafted a process for resolving patent disputes that may arise when a drug company files an ANDA seeking approval to market a generic version of an innovator drug product. Generic applicants may only trigger that process by properly serving a so-called "Paragraph IV Notice" on the innovator drug company. The law, however, is clear: generic manufacturers like Impax cannot trigger the ANDA litigation process by serving Paragraph IV Notices unless and until they have submitted an ANDA that the U.S. Food and Drug Administration ("FDA") has formally accepted as being sufficiently complete to permit substantive review. *See* 21 C.F.R. § 314.95(b). As the FDA has explained, "the [Federal Food, Drug, & Cosmetic Act ("the Act")] and legislative history . . . demonstrate that Congress

did not intend incomplete application submissions to trigger legal action . . . ." 54 Fed. Reg. 28872, 28887 (July 10, 1989).

This makes perfect sense. Allowing anything less than an ANDA that has been accepted as ready for substantive review to trigger the litigation process would wreak havoc with that process by allowing generic manufacturers to file incomplete, sham ANDAs which would nevertheless force the innovator company to litigate claims that are not – and may never become – ripe. Simply put, if an ANDA is so deficient and incomplete that the FDA is not even willing to accept it for review, there is no reason to force the courts and parties to invest the time and money required to pursue potentially unnecessary patent litigation.

In this case, it is ***undisputed*** that Impax does not have an ANDA on file that the FDA has accepted for review. Indeed, Impax itself issued a press release announcing that the FDA rescinded acceptance of its ANDA for OPANA® ER.

Impax is trying, nevertheless, to do exactly what Congress sought to prevent— to game the system and gain an unfair and unlawful advantage against Endo, Penwest and other generic manufacturers by prematurely triggering the ANDA litigation process under the Hatch-Waxman Act. Despite the fact that it has no ANDA accepted for review by the FDA, Impax inundated Endo and Penwest with no fewer than six separate Paragraph IV Notices.

Plaintiffs have asked Impax to withdraw its Paragraph IV Notices, but Impax has refused to do so. Endo and Penwest, therefore, had no practical choice but to bring this litigation to preserve their rights under the ANDA patent litigation process. Impax's actions have created a definite and concrete controversy over whether the parties must pursue this litigation now, when the patent infringement claims are premature because Impax does not have – and may never have – an ANDA accepted for review by the FDA.

The Court should put an immediate end to Impax's gamesmanship. The material facts are undisputed. Moreover, the requested declaratory relief is based on a pure question of law and goes directly to the ripeness of, and the Court's subject matter jurisdiction over, the patent infringement claims. Consequently, Endo and Penwest respectfully request that the Court issue an order declaring that:

- Impax's Paragraph IV Notices are null, void and without legal effect and it was not entitled to trigger the ANDA patent litigation process with respect to the relevant patents;
- This Court has no subject matter jurisdiction over patent infringement litigation involving the relevant patents because the Paragraph IV Notices served by Impax are null, void and of no legal effect;
- The Paragraph IV Notices served by Impax did not commence the 45-day period for filing a patent infringement action pursuant to 21 U.S.C. § 355(j)(5)(B)(iii);
- If and when the FDA accepts Impax's ANDA, Impax must submit and serve on Endo and Penwest new patent certifications at that time pursuant to 21 U.S.C. § 355(j)(2)(A)(vii).

Plaintiffs also respectfully request that the Court decide their declaratory judgment claim up-front, on an expedited basis, before the Court and the parties are put to the unnecessary expense and burden of a full-scale patent infringement case involving claims that may never need to be decided.

STATEMENT OF FACTS

A. OVERVIEW OF THE ANDA LITIGATION PROCESS

The Act provides that a company seeking to market a new pharmaceutical drug in the United States must first obtain approval from the FDA, typically through the filing of a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(a). The sponsor of the NDA is required to submit information on all patents claiming the drug that is the subject of the NDA, or a method

of using that drug, and the FDA then lists such patent information in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is commonly referred to as the "Orange Book." *See* 21 U.S.C. § 355(b)(1) and (c)(2).

On the other hand, a company seeking to market a generic version of an innovator drug is not required to submit a full NDA. Instead, it may file an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355(j). The generic drug approval process is considered "abbreviated" because the generic manufacturer may piggyback on the innovator company's data and the FDA's prior finding of safety and efficacy by demonstrating, among other things, that the generic product is bioequivalent to the previously approved drug (the "listed drug" or "innovator drug").

As part of the generic approval process, the Act provides that an ANDA filer must provide certifications addressing each of the patents listed in the Orange Book for the innovator drug at issue. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). An ANDA filer may certify, for instance, that it believes a patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4). This is known as a so-called "Paragraph IV Certification."

The sponsor of an ANDA with a Paragraph IV Certification must also provide notice to both the owner of the listed patent and the sponsor of the NDA for the listed drug. This "Paragraph IV Notice" must state that the "FDA has received an abbreviated new drug application submitted by the applicant containing any required bioavailability or bioequivalence data or information" and must also include a detailed statement of the factual and legal bases for

the applicant's belief that the challenged patent in invalid or not infringed by the proposed generic product. 21 C.F.R. § 314.95(c); *see also* 21 U.S.C. § 355(j)(2)(B).

If the patentee or NDA holder files a patent infringement action within 45 days of receiving a Paragraph IV Notice, final approval of the ANDA is generally subject to a 30-month stay. *See* 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3). The Act also provides that the first ANDA applicant to submit and lawfully maintain a Paragraph IV Certification with respect to an approved drug may be entitled to 180 days of marketing exclusivity, during which time no other ANDA filer may come to market with a competing generic product. *See* 21 U.S.C. § 355(j)(5)(B)(iv).

Timing is crucial when it comes to applying the 30-month stay and determining eligibility for the 180-day exclusivity period. The 30-month stay, for example, applies if the innovator company files an infringement action within 45 days of receiving a Paragraph IV Notice, but only if the relevant patent was submitted for listing in the Orange Book before the ANDA applicant had submitted a substantially complete ANDA. *See* 21 U.S.C. § 355(j)(5)(B)(iii). Likewise, a generic manufacturer is entitled to the 180-day market exclusivity period only if it is deemed to be a "first applicant," as determined based on the date that it has submitted "a substantially complete application that contains and lawfully maintains a [Paragraph IV Certification] for the drug." *See* 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb).

Generic applicants thus have powerful incentives to obtain the earliest filing date possible for their ANDAs, even if it requires filing a "sham" or incomplete ANDA. Congress and the FDA recognized this risk. As a result, generic applicants may not trigger the ANDA litigation process until they have an ANDA on file that has been accepted by the FDA for substantive review. *See* 21 C.F.R. § 314.95(b) ("The applicant shall send the [Paragraph IV]

notice . . . when it receives from FDA an acknowledgment letter stating that its abbreviated new drug application is sufficiently complete to permit substantive review").

B. IMPAX'S IMPROPER ATTEMPT TO TRIGGER THE ANDA LITIGATION PROCESS

The basic facts relevant to Plaintiffs' declaratory judgment claim are not in dispute:

On June 1, 2006, the FDA approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which contain oxymorphone hydrochloride, under § 505(b) of the Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. *See* http://www.fda.gov/cder/rxotcdpl/pdpl_200606.htm.[1]

Thereafter, in July 2007, the U.S. Patent & Trademark Office ("PTO") issued a Notice of Allowance for a patent application which covers the formulation of OPANA® ER. On July 23, 2007, Penwest issued a press release disclosing the Notice of Allowance. That press release described the patent "as an important component in the intellectual property estate protecting OPANA ER" and stated that "Endo will list this patent at the earliest opportunity in the Orange Book . . . ." *See* Ex. 1.

The possible listing of a new patent in the Orange Book had several important implications for Impax and any other generic manufacturer contemplating filing an ANDA with respect to OPANA® ER. First, Impax knew that once this new patent issued, Endo would be required to submit information about the patent to the FDA for listing in the Orange Book.

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[1] Pursuant to 21 U.S.C. § 355(j)(5)(F)(iii), OPANA® ER has been granted a period of regulatory exclusivity through June 22, 2009, meaning that a generic version of OPANA® ER cannot be approved for marketing before that date, even absent any patent protection.

Second, Impax also knew that if it could get an ANDA on file before that patent was submitted to the FDA, it might be able to avoid the 30-month stay on approval that typically applies to ANDAs subject to patent infringement litigation. *See* 21 U.S.C. § 355(j)(5)(B)(iii). Finally, Impax was also aware that if it was the first generic applicant to file an ANDA with a Paragraph IV Notice challenging the patent, it might be entitled to 180 days of exclusivity. In short, learning that the PTO was about to issue a new patent on OPANA® ER provided Impax with a significant incentive to rush to file an ANDA with the FDA as quickly as possible.

On October 2, 2007, the PTO issued United States Patent No. 7,276,250 ("the '250 patent"), entitled "Sustained Release Formulations Of Oxymorphone," to Penwest as assignee. *See* Ex. 2. That same day, Endo submitted information regarding the '250 patent to the FDA for listing in the Orange Book with respect to OPANA® ER tablets. *See* Ex. 3. Also on that same day, Impax sent Endo and Penwest a Paragraph IV Notice stating that it had submitted ANDA No. 79-087 seeking approval to manufacture, use, or sell a generic version of OPANA® ER prior to the expiration of the '250 patent. *See* Ex. 4.

Just two days later, however, on October 4, 2007, Impax issued a press release in which it admitted that the FDA ***"has rescinded its initial acceptance"*** of Impax's ANDA and that Impax was "working with the FDA to correct any deficiencies of the ANDA." *See* Ex. 5 (emphasis added). Despite Impax's public acknowledgement that it had no ANDA accepted for filing by the FDA, Impax continued to inundate Endo and Penwest with additional Paragraph IV Notices. On October 3, 4, 5 and 9, Impax sent to Endo and Penwest, four additional, but substantively identical notices, with respect to the '250 patent. *See* Ex. 6.

Endo and Penwest demanded that Impax withdraw its Paragraph IV Notices, but Impax has refused to do so. *See* Ex. 7. To the contrary, Impax has continued to act as if it actually had an ANDA accepted by the FDA for substantive review.

On October 19, 2007, for example, Endo submitted information regarding two additional patents – United States Patent Nos. 5,662,933 ("the '933 patent") and 5,958,456 ("the '456 patent") – to the FDA for listing in the Orange Book with respect to OPANA® ER tablets. Again, despite Impax's public acknowledgement that the FDA had rescinded acceptance of its ANDA, Impax served yet another Paragraph IV Notice on Endo and Penwest, this time with respect to the '933 and '456 patents. *See* Ex. 8.

It has now been more than six weeks since Impax publicly announced that the FDA had rescinded its ANDA, and Impax's CEO confirmed as recently as yesterday that the FDA still has not accepted for substantive review any ANDA from Impax with respect to OPANA® ER. See Ex. 9. Indeed, the FDA maintains on its website a list of all of the substantially complete ANDAs that it has on file that contain Paragraph IV Certifications, and as of the date of this brief, there is no ANDA listed on the FDA website for OPANA®ER. *See* http://www.fda.gov/cder/ogd/ppiv.htm; Ex. 10.

ARGUMENT

I. RULE 57 PROVIDES FOR EXPEDITING DECLARATORY RELIEF WHERE, AS HERE, THE CLAIM INVOLVES AN ISSUE OF LAW THAT TURNS ON UNDISPUTED FACTS

The Declaratory Judgment Act provides that "[i]n a case or actual controversy within its jurisdiction . . . any court of the United States . . . may declare the rights and other legal relations of any interested party seeking such declaration, whether or not further relief is or could be sought." 28 U.S.C. § 2201(a). To satisfy the case-or-controversy requirement, the dispute must be "definite and concrete, touching the legal relations of parties having adverse

interests" and "admit of specific relief through a decree of a conclusive character." *Medimmune, Inc. v. Genentech, Inc.*, -- U.S. --, 127 S.Ct. 764, 771 (2007) (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240-41 (1937)). "Basically, the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id.* at 771 (quoting *Maryland Casualty Co. v. Pacific Coal & Oil, Co.*, 312 U.S. 270, 273 (1941)).

Rule 57 of the Federal Rules of Civil Procedure specifically provides for expediting declaratory judgment relief. *See* Fed. R. Civ. P. 57 ("The Court may order a speedy hearing of an action for a declaratory judgment and may advance it on the calendar."). Indeed, Rule 57 is "specifically designed to 'afford a speedy and inexpensive method of adjudicating legal disputes to settle legal rights and remove uncertainty and insecurity from legal relationships. . . .'" *Rechler P'Ship v. Resolution Trust Corp.*, 1990 WL 711357, at *7 (D.N.J. Sept. 7, 1990) (quoting *Beacon Constr. Co., Inc. v. Matco Elec. Co., Inc.*, 521 F.2d 392, 397 (2d Cir. 1975)). Courts have recognized that expedited relief is appropriate where – as here – the claim involves "an issue of law on undisputed or relatively undisputed facts." *Rechler*, 1990 WL 711357, at *7 (quoting Advisory Committee Notes to Rule 57) (granting expedited relief where "essential fact" was "undisputed" and issue was "purely legal"); *see also Pence v. Lexington Ins. Co.*, 2006 WL 133475, at *2 (S.D. Tex. Jan. 17, 2006) ("a declaratory judgment is appropriate when it will 'terminate the controversy' giving rise on undisputed or relatively undisputed facts and it operates frequently as a summary proceeding") (quoting Advisory Committee Notes).

Expedited relief is particularly appropriate here because resolution of the controversy between Plaintiffs and Impax turns on a pure legal issue: Whether Impax has

properly triggered the Hatch-Waxman ANDA litigation process. That legal issue can be resolved based upon a single ***undisputed*** fact—that Impax does not have an ANDA for OPANA® ER that the FDA has accepted for substantive review. It requires neither discovery, nor an evidentiary hearing.

It also makes sense to resolve this dispute quickly, at the start of the case, because it goes directly to the threshold question of whether the Court has subject matter jurisdiction to hear Endo and Penwest's patent infringement claims. Under 35 U.S.C. § 271, it is an act of infringement to submit an ANDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of a drug claimed in a patent before the expiration of such patent. *See* 35 U.S.C. § 271(e)(2). The Supreme Court has explained that Congress created this "artificial" act of infringement in § 271(e)(2) solely to "enable the judicial adjudication upon which the ANDA . . . scheme[] depend[s]." *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990). That scheme, however, cannot begin until the FDA has accepted an ANDA for substantive review. Accordingly, without an accepted ANDA, it follows that there is no act of infringement under 35 U.S.C. § 271(e). Here, it undisputed that Impax does not have an accepted ANDA on file with the FDA, and thus the Court has no jurisdiction over any latent patent claims. Thus, Plaintiffs' requested declaratory judgment relief is incident to the Court's inherent power to "guard its jurisdiction jealously." *Merck & Co., Inc. v. Apotex, Inc.*, 488 F. Supp. 2d 418, 424 (D. Del. 2007).

II. THE COURT SHOULD GRANT PLAINTIFFS' REQUESTED DECLARATORY RELIEF BECAUSE IMPAX'S PARAGRAPH IV CERTIFICATIONS ARE NULL AND VOID

A. Absent An ANDA That Has Been Accepted By The FDA, A Generic Manufacturer Has No Legitimate Basis To Trigger The ANDA Litigation Process

FDA regulations clearly provide that absent an ANDA that has been accepted by the FDA for substantive review, generic manufacturers have no legitimate basis to initiate the ANDA litigation process. *See* 21 C.F.R. 314.95(b). This safeguard makes sense, given the incentives for generic applicants to jump the gun by filing incomplete ANDAs in order to obtain the earliest possible filing date. A generic applicant that is able to file its ANDA before the listing of a patent in the Orange Book may be able to avoid application of a 30-month stay of approval. Likewise, a generic applicant deemed to be a "first filer" gets the advantage of 180 days of marketing exclusivity.

Congress was well aware of, and sought to minimize, this potential for abuse. The legislative history of the Act, for instance, leaves no doubt that Congress considered the FDA's acceptance for substantive review of a valid, substantially complete ANDA to be a prerequisite for starting the ANDA litigation process. A House Report discussing the Paragraph IV Notice requirement specifically states that "the committee does not intend that applicants be permitted to circumvent this notice requirement by filing sham ANDA's or ANDA's which are substantially incomplete." H.R. Rep. 98-857(I), at 24, *reprinted in* 1984 U.S.C.C.A.N. 2647, 2657 (Ex. 11). In the context of discussing a failure to include bioequivalence tests, the legislative history further explains that an incomplete ANDA "will void the effectiveness of any notice" and that "notice must then be given again" if a complete ANDA is later submitted. *Id.* at 25, 2658.

Moreover, the FDA has confirmed that it adopted 21 C.F.R. § 314.95(b) to give effect to Congress's intent that a generic manufacturer such as Impax be permitted to trigger the litigation process only if it has submitted an ANDA that the FDA has accepted for substantive review. As the FDA explained at the time it proposed that regulation, "the statute and legislative history . . . demonstrate that ***Congress did not intend incomplete application submissions to trigger legal action*** by a patent owner or approved application holder." 54 Fed. Reg. 28872, 28887 (July 10, 1989) (emphasis added). Following a lengthy comment period, the FDA approved the regulation without making any changes to subsection (b). In the adopting release, the FDA echoed its earlier rationale for the regulation:

> To permit an ANDA applicant to provide notice before FDA has determined whether the ANDA is sufficiently complete would be contrary to the legislative history because it would only encourage ANDA applicants to file incomplete or "sham" ANDA's and to supplement them later to secure a place in the review queue in an attempt to secure the first ANDA approval.

59 Fed. Reg. 50338, 50350 (Oct. 3, 1994).

B. The Undisputed Facts Demonstrate That Impax Had No Basis To Trigger The ANDA Litigation Process And That Plaintiffs Are Entitled As A Matter Of Law To The Declaratory Relief They Seek

Here, the undisputed facts demonstrate beyond question that Impax is playing games with the carefully constructed statutory and regulatory framework. Indeed, a single undisputed fact – that Impax did not have and still does not have an accepted ANDA on file with FDA – justifies the declaratory relief the Plaintiffs seek.

Despite admitting that the FDA rescinded acceptance of its ANDA, Impax has persisted in its efforts to push the ANDA litigation process forward. It has refused to withdraw its original Paragraph IV Notice, which was served the very day the '250 patent issued (*i.e.*,

before FDA even had time to include that patent in the electronic Orange Book listing), and it continued thereafter to serve several such notices on a daily basis.

By racing to file an incomplete ANDA, Impax hoped to preempt application of the 30-month stay (by filing before the listing of the '250 patent) and to co-opt for itself the 180-day market exclusivity afforded the first ANDA applicant to successfully challenge a listed patent. The problem is that in its race to game the system, Impax was unable to compile and submit a substantially complete ANDA.

As a result, Impax has no legitimate basis to trigger the ANDA patent infringement litigation process. Each of the Paragraph IV Notices Impax sent to Endo and Penwest beginning on October 2, 2007 was improper, null, void, and without legal effect. This Court should put an end to Impax's flagrant abuse of the ANDA litigation process, and grant Plaintiffs' the declaratory judgment they seek.

The appropriate path forward is clear. Plaintiffs respectfully request that the Court declare that Impax's efforts to trigger the ANDA patent litigation process were premature and that Impax's Paragraph IV Notices are null, void and of no legal effect. Upon doing so, the Court can dismiss the Plaintiffs' patent infringement claims as moot. ***If*** the FDA were, at some point, to accept Impax's ANDA for filing, that would be the appropriate time for Impax to trigger the Paragraph IV litigation process, assuming it had a good faith basis to do so.

Moreover, the Court should grant Plaintiffs' requested declaratory relief immediately. The propriety of Impax's misguided attempts to trigger the ANDA litigation process goes to the very heart of this Court's subject matter jurisdiction over the patent infringement claims that Impax, by its actions, forced Plaintiffs to include in their complaint to

preserve their rights under the Act.[2] Without a valid ANDA accepted and on file with the FDA, there is no act of infringement under 35 U.S.C. § 271(e), and thus, the Court has no jurisdiction over those latent patent claims. Indeed, if Impax is unable to fix the deficiencies that caused the FDA to rescind acceptance of its ANDA, those claims may never need to be litigated. Accordingly, the Court should grant the declaratory relief Plaintiffs seek, and dismiss those patent claims as moot before it and Plaintiffs are forced to incur any more time and expense on this matter.

CONCLUSION

For all of the above reasons, Endo and Penwest respectfully request that the Court grant their motion and enter the proposed order submitted herewith.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

Jack B. Blumenfeld (#1014)
Mary B. Graham (#2256)
Julia Heaney (#3052)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 1999
(302) 658-9200
jblumenfeld@mnat.com
mgraham@mnat.com
jheaney@mnat.com
Attorneys for Plaintiffs
Endo Pharmaceuticals Inc. and
Penwest Pharmaceuticals Co.

[2] For these reasons, this case is far different than *Minnesota Mining and Manuf. Co. v. Barr Labs, Inc.*, 289 F.3d 775 (Fed Cir. 2002), in which the Federal Circuit declined to review the sufficiency of a Paragraph IV Notice. That case involved a challenge to the sufficiency of the content of a Paragraph IV Notice for purposes of determining infringement. Here, by contrast, the issue is not the content of Impax's Paragraph IV Notice, but rather whether or not the necessary predicate condition for triggering the ANDA litigation process – and this Court's subject matter jurisdiction – exists in the first place.

Of Counsel:

Martin J. Black
George G. Gordon
Ann M. Caviani Pease
Robert D. Rhoad
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
(215) 994-4000

Robert J. Gunther, Jr.
Lisa J. Pirozzolo
James P. Barabas
WILMER CUTLER PICKERING HALE AND DORR LLP
399 Park Avenue
New York, NY 10022
(212) 230-8800

November 20, 2007

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on November 20, 2007 I electronically filed the foregoing with the Clerk of the Court using CM/ECF.

I further certify that true and correct copies of the foregoing were caused to be served on November 20, 2007 upon the following individuals in the manner indicated:

VIA HAND DELIVERY

Impax Laboratories, Inc.
c/o The Prentice-Hall Corp. Systems, Inc.
2711 Centerville Road
Suite 400
Wilmington, DE 19808

VIA ELECTRONIC MAIL

Daralyn Durie, Esquire
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 97111-1704

Jack B. Blumenfeld (#1014)
jblumenfeld@mnat.com

EXHIBIT 1

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Penwest Announces Allowance for Oxymorphone Patent Application Related to OPANA ER

DANBURY, Conn., Jul 23, 2007 (PrimeNewswire via COMTEX News Network) -- Penwest Pharmaceuticals Co. (Nasdaq:PPCO) today reported that the U.S. Patent and Trademark Office (PTO) has indicated on its website that a Penwest patent application claiming the sustained-release formulation of oxymorphone related to OPANA(r) ER (oxymorphone HCl) extended-release tablets CII has been allowed.

Penwest previously announced that it received a final rejection from the PTO for this application on March 15, 2007. In response to the rejection, the Company amended the claims and the PTO examiner found these amended claims allowable.

OPANA ER uses Penwest's TIMERx(r) technology and is indicated for the treatment of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. OPANA ER is not intended to be used on an as-needed basis. It is marketed by Endo Pharmaceuticals Inc.

"We are very pleased that this patent application related to OPANA ER has been allowed by the U.S. Patent and Trademark Office," said Jennifer L. Good, President and Chief Executive Officer of Penwest. "We believe that this patent is an important component in the intellectual property estate protecting OPANA ER."

Upon payment of the issue fee, the PTO will prepare the allowed patent application for printing and publication. The patent, once issued, will be scheduled to expire in 2022. Penwest expects that Endo will list this patent at the earliest opportunity in the Orange Book published by the U.S. Food and Drug Administration (FDA).

Penwest Pharmaceuticals

Penwest is a specialty pharmaceutical company dedicated to bringing to the marketplace innovative products that help improve the lives of patients. The Company's goal is to identify, develop and commercialize prescription products that address unmet medical needs, primarily for diseases of the nervous system. The launch by Endo Pharmaceuticals in mid-2006 of OPANA(r) ER (oxymorphone hydrochloride extended-release tablets) formulated with the Company's TIMERx(r) extended release delivery technology demonstrates the execution of this strategy and the value of the Company's TIMERx(r) technology. The Company is currently applying its expertise to a pipeline of potential products that are in various stages of development. The Company intends to commercialize these products independently or through third party alliances.

Penwest Forward-Looking Statement

The matters discussed herein contain forward-looking statements that involve risks and uncertainties, which may cause Penwest's actual results in future periods to be materially different from any future performance suggested herein. For this purpose, any statements contained herein that are not statements of historical fact may be deemed to be forward-looking statements. Without limiting the foregoing, the words "believes," "anticipates," "plans," "expects," "intends," "potential," and similar expressions are intended to identify forward-looking statements. Important factors that could cause results to differ materially include: risks relating to the commercial success of OPANA ER and our reliance on Endo for the commercial success of OPANA ER; regulatory risks relating to drugs in development, including the timing and outcome of regulatory action; uncertainty of success of collaborations including the collaboration with Edison Pharmaceuticals; the timing of clinical trials, including the impact of enrollment rates; whether the results of clinical trials will warrant further clinical trials or warrant submission of an application for regulatory approval of, or the regulatory approval of, the product that is the subject of the trial; actual and potential competition; the need for capital; and other risks as set forth under the caption Risk Factors in Penwest's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 10, 2007, which risk factors are incorporated herein by reference.

The forward-looking statements contained in this press release speak only as of the date of the statement made. Penwest disclaims any intention or obligation to update any forward-looking statements. TIMERx is a registered trademark of Penwest. All other trademarks referenced herein are the property of their respective owners.

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SOURCE: Penwest Pharmaceuticals Co.

Penwest Pharmaceuticals Co.
Investors:
Ben Palleiko
(203) 796-3750
(877) 736-9378

Kekst and Company
Media:
Laura Walters
(212) 521-4800

EXHIBIT 2

(12) **United States Patent**
Baichwal et al.

(10) **Patent No.: US 7,276,250 B2**
(45) **Date of Patent: Oct. 2, 2007**

(54) **SUSTAINED RELEASE FORMULATIONS OF OXYMORPHONE**

(75) Inventors: **Anand R. Baichwal**, Wappingers Falls, NY (US); **Huai-Hung Kao**, Syosset, NY (US); **Troy W. McCall**, Germantown, TN (US)

(73) Assignee: **Penwest Pharmaceuticals Company**, Danbury, CT (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 216 days.

(21) Appl. No.: **10/189,932**

(22) Filed: **Jul. 3, 2002**

(65) **Prior Publication Data**

US 2003/0129230 A1 Jul. 10, 2003

Related U.S. Application Data

(60) Provisional application No. 60/329,352, filed on Oct. 15, 2001, provisional application No. 60/329,426, filed on Oct. 15, 2001, provisional application No. 60/303,357, filed on Jul. 6, 2001.

(51) **Int. Cl.**
A61K 9/22 (2006.01)
A61K 9/26 (2006.01)
A61K 9/36 (2006.01)

(52) **U.S. Cl.** **424/468**; 424/470; 424/464; 424/479; 424/480; 424/481; 424/482

(58) **Field of Classification Search** 424/468, 424/474, 490, 475, 476, 477, 479, 480, 482, 424/491, 494, 495, 497, 498
See application file for complete search history.

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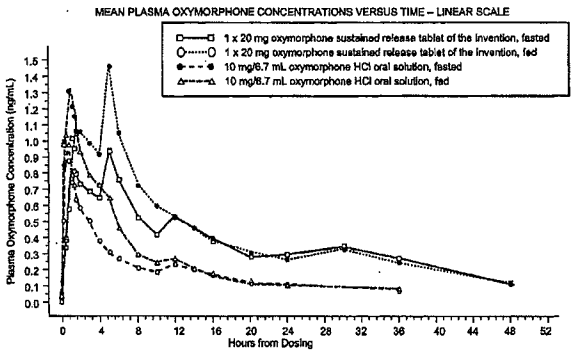
Primary Examiner—Lakshmi S. Channavajjala
(74) *Attorney, Agent, or Firm*—Wilmer Cutler Pickering Hale & Dorr, LLP

(57) **ABSTRACT**

Sustained release formulations of oxymorphone or pharmaceutically acceptable salts thereof; methods for making the sustained release formulations of oxymorphone or pharmaceutically acceptable salts thereof; and methods for using the sustained release formulations of oxymorphone or pharmaceutically acceptable salts thereof to treat patients suffering from pain are provided.

16 Claims, 1 Drawing Sheet



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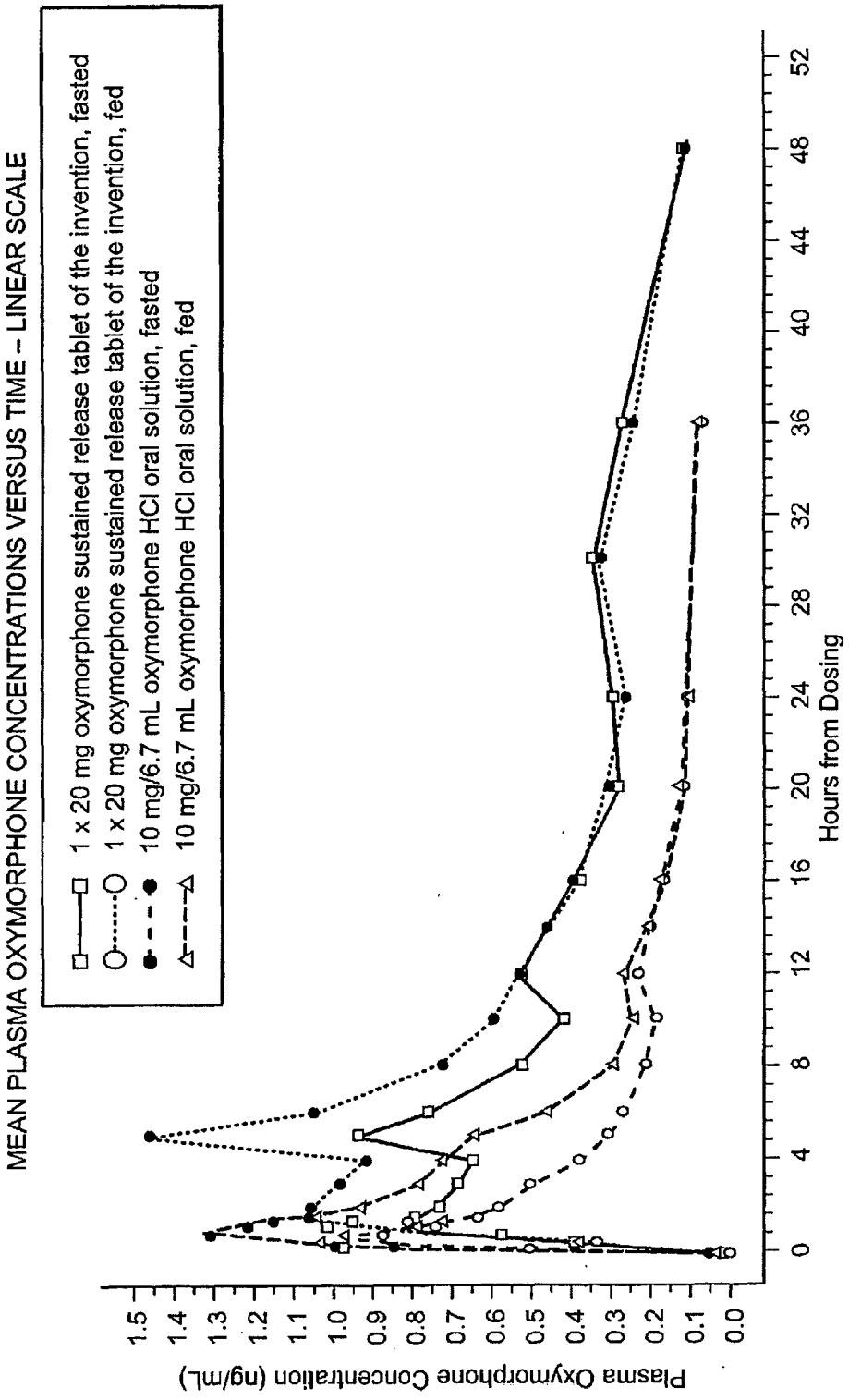

MEAN PLASMA OXYMORPHONE CONCENTRATIONS VERSUS TIME – LINEAR SCALE
1 x 20 mg oxymorphone sustained release tablet of the invention, fasted
1 x 20 mg oxymorphone sustained release tablet of the invention, fed
10 mg/6.7 mL oxymorphone HCl oral solution, fasted
10 mg/6.7 mL oxymorphone HCl oral solution, fed
Plasma Oxymorphone Concentration (ng/mL)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
Hours from Dosing
0
4
8
12
16
20
24
28
32
36
40
44
48
52

SUSTAINED RELEASE FORMULATIONS OF OXYMORPHONE

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/329,426 filed Oct. 15, 2001, U.S. Provisional Application No. 60/329,352 filed Oct. 15, 2001, and to U.S. Provisional Application No. 60/303,357 filed Jul. 6, 2001, the disclosures of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The invention provides sustained release formulations of oxymorphone and pharmaceutically acceptable salts thereof; methods for making the sustained release formulations of oxymorphone and pharmaceutically acceptable salts thereof; and methods for using the sustained release formulations of oxymorphone and pharmaceutically acceptable salts thereof to treat patients suffering from pain.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the United States suffer from severe pain that is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely used for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, a 10 mg oral immediate release tablet formation of oxymorphone HCl was marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6 alpha and beta hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. Scheduled rather than "as needed" administration of opioids is currently recommended in guidelines for their use in treating chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate 4-hourly administrations in order to maintain optimal levels of analgesia in patients with chronic pain. Moreover, immediate release oxymorphone exhibits low oral bioavailability, because oxymorphone is extensively metabolized in the liver.

There is a need in the art for new formulations of oxymorphone that require less frequent dosing. The invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The invention provides compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, where the sustained release delivery system comprises at least one hydrophilic compound, at least one cross-linking agent (which may be cationic) and at least one pharmaceutical diluent. The sustained release delivery system may further comprise one or more additional hydrophobic polymers or cross-linking compounds. The compositions may optionally comprise an outer coating comprising at least one water insoluble compound, and optionally one or more plasticizers and/or water soluble compounds.

The invention provides compositions comprising an inner core and an outer sustained release coating, where the inner core comprises oxymorphone or a pharmaceutically acceptable salt thereof and the outer sustained release coating comprises at least one water insoluble compound. The outer sustained release coating may optionally further comprise one or more plasticizers and/or water soluble compounds.

The invention provides methods for treating pain in patients by administering an effective amount of any of the compositions of the invention. The pain may be moderate to severe, and may be acute or chronic.

The invention also provides methods for making such compositions.

These and other aspects of the invention are described in detail herein.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 is a linear scale graph, without standard deviations, showing the mean oxymorphone plasma concentration versus time for patients treated with the sustained release oxymorphone tablets of the invention after fasting (A), for patients treated with sustained release oxymorphone tablets of the invention after a high fat meal (B), for patients treated with an oxymorphone solution after fasting (C), and for patients treated with an oxymorphone solution after a high fat meal (D).

DETAILED DESCRIPTION OF THE INVENTION

To overcome the difficulties associated with the very low bioavailability of the oral immediate release formulation of oxymorphone and with a 4 hourly dosing frequency of oxymorphone, the invention provides an oral sustained release formulation of oxymorphone comprising an analgesically effective amount of oxymorphone or a pharmaceutically acceptable salt thereof. The bioavailability of the oral sustained release formulations of the invention is sufficiently high that the sustained release formulations can be used to treat patients suffering from pain with only once or twice daily dosing.

The invention provides compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, wherein the sustained release delivery system comprises (i) at least one hydrophilic compound, at least one cross-linking agent, and at least one pharmaceutical diluent; (ii) at least one hydrophilic compound, at least one cross-linking agent, at least one pharmaceutical diluent, and at least one hydrophobic polymer; (iii) at least one hydrophilic compound, at least one cross-linking agent, at least one pharmaceutical diluent, and at least one cationic cross-linking agent different from the

first cross-linking agent; (iv) at least one hydrophilic compound, at least one cross-linking agent, at least one pharmaceutical diluent, at least one cationic cross-linking compound different from the first cross-linking agent, and at least one hydrophobic polymer; (v) at least one hydrophilic compound, at least one cationic cross-linking compound, and at least one pharmaceutical diluent; or (vi) at least one hydrophilic compound, at least one cationic cross-linking compound, at least one pharmaceutical diluent, and at least one hydrophobic compound.

The oxymorphone may be homogeneously dispersed in the sustained release delivery system. Preferably, the oxymorphone or pharmaceutically acceptable salt thereof may be present in the composition in an amount of about 1 mg to about 200 mg, more preferably in an amount of about 1 mg to about 100 mg, even more preferably in an amount of about 5 mg to about 80 mg. Preferably, the sustained release delivery system may be present in the composition in an amount from about 80 mg to about 420 mg, more preferably from about 80 mg to about 360 mg, even more preferably from about 80 mg to about 200 mg. "Oxymorphone" includes oxymorphone, metabolites thereof, derivatives thereof, and/or pharmaceutically acceptable salts thereof. Metabolites of oxymorphone include, for example, 6-hydroxy-oxymorphone (e.g., 6-α-hydroxy-oxymorphone and/or 6-β-hydroxy-oxymorphone).

Oxymorphone may be in the form of any pharmaceutically acceptable salt known in the art. Exemplary pharmaceutically acceptable salts include hydrochloric, sulfuric, nitric, phosphoric, hydrobromic, maleric, malic, ascorbic, citric, tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, napthalinesulfonic, linoleic, linolenic acid, and the like. The hydrochloride salt of oxymorphone is preferred.

The sustained release delivery system comprises at least one hydrophilic compound. The hydrophilic compound preferably forms a gel matrix that releases the oxymorphone or the pharmaceutically acceptable salt thereof at a sustained rate upon exposure to liquids. The rate of release of the oxymorphone or the pharmaceutically acceptable salt thereof from the gel matrix depends on the drug's partition coefficient between the components of the gel matrix and the aqueous phase within the gastrointestinal tract. In the compositions of the invention, the weight ratio of oxymorphone to hydrophilic compound is generally in the range of about 1:0.5 to about 1:25, preferably in the range of about 1:0.5 to about 1:20. The sustained release delivery system generally comprises the hydrophilic compound in an amount of about 20% to about 80% by weight, preferably in an amount of about 20% to about 60% by weight, more preferably in an amount of about 40% to about 60% by weight, still more preferably in an amount of about 50% by weight.

The hydrophilic compound may be any known in the art. Exemplary hydrophilic compounds include gums, cellulose ethers, acrylic resins, polyvinyl pyrrolidone, protein-derived compounds, and mixtures thereof. Exemplary gums include heteropolysaccharide gums and homopolysaccharide gums, such as xanthan, tragacanth, pectins, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean gums, and gellan gums. Exemplary cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses. Preferred cellulose ethers include hydroxyethyl celluloses, hydroxypropyl celluloses, hydroxypropylmethyl-celluloses, carboxy methylcelluloses, and mixtures thereof. Exemplary acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. In some embodiments, the hydrophilic compound is preferably a gum, more preferably a heteropolysaccharide gum, most preferably a xanthan gum or derivative thereof. Derivatives of xanthan gum include, for example, deacylated xanthan gum, the carboxymethyl esters of xanthan gum, and the propylene glycol esters of xanthan gum.

In another embodiment, the sustained release delivery system may further comprise at least one cross-linking agent. The cross-linking agent is preferably a compound that is capable of cross-linking the hydrophilic compound to form a gel matrix in the presence of liquids. As used herein, "liquids" includes, for example, gastrointestinal fluids and aqueous solutions, such as those used for in vitro dissolution testing. The sustained release delivery system generally comprises the cross-linking agent in an amount of about 0.5% to about 80% by weight, preferably in an amount of about 2% to about 54% by weight, more preferably in an amount of about 20% to about 30% by weight more, still more preferably in an amount of about 25% by weight.

Exemplary cross-linking agents include homopolysaccharides. Exemplary homopolysaccharides include galactomannan gums, such as guar gum, hydroxypropyl guar gum, and locust bean gum. In some embodiments, the cross-linking agent is preferably a locust bean gum or a guar gum. In other embodiments, the cross-linking agents may be alginic acid derivatives or hydrocolloids.

When the sustained release delivery system comprises at least one hydrophilic compound and at least one cross-linking agent, the ratio of hydrophilic compound to cross-linking agent may be from about 1:9 to about 9:1, preferably from about 1:3 to about 3:1.

The sustained release delivery system of the invention may comprise one or more cationic cross-linking compounds. Cationic cross-linking compound may be used instead of or in addition to the cross-linking agent. The cationic cross-linking compounds may be used in an amount sufficient to cross-link the hydrophilic compound to form a gel matrix in the presence of liquids. The cationic cross-linking compound is present in the sustained release delivery system in an amount of about 0.5% to about 30% by weight, preferably from about 5% to about 20% by weight.

Exemplary cationic cross-linking compounds include monovalent metal cations, multivalent metal cations, and inorganic salts, including alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, and mixtures thereof. For example, the cationic cross-linking compound may be one or more of calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, or mixtures thereof.

When the sustained release delivery system comprises at least one hydrophilic compound and at least one cationic cross-linking compound, the ratio of hydrophilic compound to cationic cross-linking compound may be from about 1:9 to about 9:1, preferably from about 1:3 to about 3:1.

Two properties of desirable components of this system (e.g., the at least one hydrophilic compound and the at least one cross-linking agent; or the at least one hydrophilic compound and at least one cationic cross-linking compound) that form a gel matrix upon exposure to liquids are fast hydration of the compounds/agents and the ability to form a gel matrix having a high gel strength. These two properties, which are needed to achieve a slow release gel matrix, are maximized in the invention by the particular combination of compounds (e.g., the at least one hydrophilic compound and

the at least one cross-linking agent; or the at least one hydrophilic compound and the at least one cationic cross-linking compound). For example, hydrophilic compounds (e.g., xanthan gum) have excellent water-wicking properties which provide fast hydration. The combination of hydrophilic compounds with materials that are capable of cross-linking the rigid helical ordered structure of the hydrophilic compound (e.g., cross-linking agents and/or cationic cross-linking compounds) thereby act synergistically to provide a higher than expected viscosity (i.e., high gel strength) of the gel matrix.

The sustained release delivery system further comprises one or more pharmaceutical diluents known in the art. Exemplary pharmaceutical diluents include monosaccharides, disaccharides, polyhydric alcohols and mixtures thereof. Preferred pharmaceutical diluents include, for example, starch, lactose, dextrose, sucrose, microcrystalline cellulose, sorbitol, xylitol, fructose, and mixtures thereof. In other embodiments, the pharmaceutical diluent is water-soluble, such as lactose, dextrose, sucrose, or mixtures thereof. The ratio of pharmaceutical diluent to hydrophilic compound is generally from about 1:8 to about 8:1, preferably from about 1:3 to about 3:1. The sustained release delivery system generally comprises one or more pharmaceutical diluents in an amount of about 20% to about 80% by weight, preferably about 35% by weight. In other embodiments, the sustained release delivery system comprises one or more pharmaceutical diluents in an amount of about 40% to about 80% by weight.

The sustained release delivery system of the invention may comprise one or more hydrophobic polymers. The hydrophobic polymers may be used in an amount sufficient to slow the hydration of the hydrophilic compound without disrupting it. For example, the hydrophobic polymer may be present in the sustained release delivery system in an amount of about 0.5% to about 20% by weight, preferably in an amount of about 2% to about 10% by weight, more preferably in an amount of about 3% to about 7% by weight, still more preferably in an amount of about 5% by weight.

Exemplary hydrophobic polymers include alkyl celluloses (e.g., C_{1-6} alkyl celluloses, carboxymethylcellulose), other hydrophobic cellulosic materials or compounds (e.g., cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate), polyvinyl acetate polymers (e.g., polyvinyl acetate phthalate), polymers or copolymers derived from acrylic and/or methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and mixtures thereof. The hydrophobic polymer is preferably methyl cellulose, ethyl cellulose or propyl cellulose, more preferably ethyl cellulose.

The compositions of the invention may be further admixed with one or more wetting agents (such as polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil, polyethoxylated fatty acid from hydrogenated castor oil) one or more lubricants (such as magnesium stearate, sodium stearyl fumarate, and the like), one or more buffering agents, one or more colorants, and/or other conventional ingredients.

In other embodiments, the invention provides oral sustained release solid dosage formulations comprising from about 1 mg to 200 mg oxymorphone hydrochloride, preferably from about 5 mg to about 80 mg oxymorphone hydrochloride; and about 80 mg to about 200 mg of a sustained release delivery system, preferably from about 120 mg to about 200 mg of a sustained release delivery system, more preferably about 160 mg of a sustained release delivery system; where the sustained release delivery system comprises about 8.3 to about 41.7% locust bean gum, preferably about 25% locust bean gum; about 8.3 to about 41.7% xanthan gum, preferably about 25% xanthan gum; about 20 to about 55% dextrose, preferably about 35% dextrose; about 5 to about 20% calcium sulfate dihydrate, preferably about 10% calcium sulfate dihydrate; and about 2 to 10% ethyl cellulose, preferably about 5% ethyl cellulose.

In other embodiments, the invention provides oral sustained release solid dosage formulations comprising from about 1 mg to 200 mg oxymorphone hydrochloride, preferably from about 5 mg to about 80 mg oxymorphone hydrochloride; and about 200 mg to about 420 mg of a sustained release delivery system, preferably from about 300 mg to about 420 mg of a sustained release delivery system, more preferably about 360 mg of a sustained release delivery system; where the sustained release delivery system comprises about 8.3 to about 41.7% locust bean gum, preferably about 25% locust bean gum; about 8.3 to about 41.7% xanthan gum, preferably about 25% xanthan gum; about 20 to about 55% dextrose, preferably about 35% dextrose; about 5 to about 20% calcium sulfate dihydrate, preferably about 10% calcium sulfate dihydrate; and about 2 to 10% ethyl cellulose, preferably about 5% ethyl cellulose.

The sustained release formulations of oxymorphone are preferably orally administrable solid dosage formulations which may be, for example, tablets, capsules comprising a plurality of granules, sublingual tablets, powders, or granules; preferably tablets. The tablets may be an enteric coating or a hydrophilic coating.

The sustained release delivery system in the compositions of the invention may be prepared by dry granulation or wet granulation, before the oxymorphone or pharmaceutically acceptable salt thereof is added, although the components may be held together by an agglomeration technique to produce an acceptable product. In the wet granulation technique, the components (e.g., hydrophilic compounds, cross-linking agents, pharmaceutical diluents, cationic cross-linking compounds, hydrophobic polymers, etc.) are mixed together and then moistened with one or more liquids (e.g., water, propylene glycol, glycerol, alcohol) to produce a moistened mass which is subsequently dried. The dried mass is then milled with conventional equipment into granules of the sustained release delivery system. Thereafter, the sustained release delivery system is mixed in the desired amounts with the oxymorphone or the pharmaceutically acceptable salt thereof and, optionally, one or more wetting agents, one or more lubricants, one or more buffering agents, one or more coloring agents, or other conventional ingredients, to produce a granulated composition. The sustained release delivery system and the oxymorphone may be blended with, for example, a high shear mixer. The oxymorphone is preferably finely and homogeneously dispersed in the sustained release delivery system. The granulated composition, in an amount sufficient to make a uniform batch of tablets, is subjected to tableting in a conventional production scale tableting machine at normal compression pressures, i.e., about 2,000-16,000 psi. The mixture should not be compressed to a point where there is subsequent difficulty with hydration upon exposure to liquids.

The average particle size of the granulated composition is from about 50 μm to about 400 μm, preferably from about 185 μm to about 265 μm. The average density of the granulated composition is from about 0.3 g/ml to about 0.8 g/ml, preferably from about 0.5 g/ml to about 0.7 g/ml. The tablets formed from the granulations are generally from about 6 to about 8 kg hardness. The average flow of the granulations are from about 25 to about 40 g/sec.

In other embodiments, the invention provides sustained release coatings over an inner core comprising oxymorphone or a pharmaceutically acceptable salt thereof. For example, the inner core comprising oxymorphone or a pharmaceutically acceptable salt thereof may be coated with a sustained release film which, upon exposure to liquids, releases the oxymorphone or the pharmaceutically acceptable salt thereof from the core at a sustained rate.

In one embodiment, the sustained release coating comprises at least one water insoluble compound. The water insoluble compound is preferably a hydrophobic polymer. The hydrophobic polymer may be the same as or different from the hydrophobic polymer used in the sustained release delivery system. Exemplary hydrophobic polymers include alkyl celluloses (e.g., C_{1-6} alkyl celluloses, carboxymethylcellulose), other hydrophobic cellulosic materials or compounds (e.g., cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate), polyvinyl acetate polymers (e.g., polyvinyl acetate phthalate), polymers or copolymers derived from acrylic and/or methacrylic acid esters, zein, waxes (alone or in admixture with fatty alcohols), shellac, hydrogenated vegetable oils, and mixtures thereof. The hydrophobic polymer is preferably, methyl cellulose, ethyl cellulose or propyl cellulose, more preferably ethyl cellulose. The sustained release formulations of the invention may be coated with a water insoluble compound to a weight gain from about 1 to about 20% by weight.

The sustained release coating may further comprise at least one plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, polyethylene glycol, or mixtures thereof.

The sustained release coating may also contain at least one water soluble compound, such as polyvinylpyrrolidones, hydroxypropylmethylcelluloses, or mixtures thereof. The sustained release coating may comprise at least one water soluble compound in an amount from about 1% to about 6% by weight, preferably in an amount of about 3% by weight.

The sustained release coating may be applied to the oxymorphone core by spraying an aqueous dispersion of the water insoluble compound onto the oxymorphone core. The oxymorphone core may be a granulated composition made, for example, by dry or wet granulation of mixed powders of oxymorphone and at least one binding agent; by coating an inert bead with oxymorphone and at least one binding agent; or by spheronizing mixed powders of oxymorphone and at least one spheronizing agent. Exemplary binding agents include hydroxypropylmethylcelluloses. Exemplary spheronizing agents include microcrystalline celluloses. The inner core may be a tablet made by compressing the granules or by compressing a powder comprising oxymorphone or the pharmaceutically acceptable salt thereof.

In other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with a sustained release coating, as described herein. In still other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with a hydrophobic polymer, as described herein. In still other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with an enteric coating, such as cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimelliate, or mixtures thereof. In still other embodiments, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, are coated with a hydrophobic polymer, as described herein, and further coated with an enteric coating, as described herein. In any of the embodiments described herein, the compositions comprising oxymorphone or a pharmaceutically acceptable salt thereof and a sustained release delivery system, as described herein, may optionally be coated with a hydrophilic coating which may be applied above or beneath the sustained release film, above or beneath the hydrophobic coating, and/or above or beneath the enteric coating. Preferred hydrophilic coatings comprise hydroxypropylmethylcellulose.

The invention provides methods for treating pain by administering an effective amount of the sustained release formulations of oxymorphone to a patient in need thereof. An effective amount is an amount sufficient to eliminate all pain or to alleviate the pain (i.e., reduce the pain compared to the pain present prior to administration of the oxymorphone sustained release formulation). "Sustained release" means that the oxymorphone or pharmaceutically acceptable salt thereof is released from the formulation at a controlled rate so that therapeutically beneficial blood levels (but below toxic levels) of the oxymorphone or pharmaceutically acceptable salt thereof are maintained over an extended period of time. The sustained release formulations of oxymorphone are administered in an amount sufficient to alleviate pain for an extended period of time, preferably about 8 hours to about 24 hours, more preferably for a period of about 12 hours to about 24 hours. The oxymorphone sustained release oral solid dosage formulations of the invention may be administered one to four times a day, preferably once or twice daily, more preferably once daily. The pain may be minor to moderate to severe, and is preferably moderate to severe. The pain may be acute or chronic. The pain may be associated with, for example, cancer, autoimmune diseases, infections, surgical traumas, accidental traumas or osteoarthritis. The patient may be an animal, preferably a mammal, more preferably a human.

In certain embodiments, upon oral ingestion of the oxymorphone sustained release formulation and contact of the formulation with gastrointestinal fluids, the sustained release formulation swells and gels to form a hydrophilic gel matrix from which the oxymorphone is released. The swelling of the gel matrix causes a reduction in the bulk density of the formulation and provides the buoyancy necessary to allow the gel matrix to float on the stomach contents to provide a slow delivery of the oxymorphone. The hydrophilic matrix, the size of which is dependent upon the size of the original formulation, can swell considerably and become obstructed near the opening of the pylorus. Since the oxymorphone is dispersed throughout the formulation (and consequently throughout the gel matrix), a constant amount of oxymorphone can be released per unit time in vivo by dispersion or erosion of the outer portions of the hydrophilic gel matrix. The process continues, with the gel matrix remaining bouyant in the stomach, until substantially all of the oxymorphone is released.

In certain embodiments, the chemistry of certain of the components of the formulation, such as the hydrophilic compound (e.g., xanthan gum), is such that the components are considered to be self-buffering agents which are substantially insensitive to the solubility of the oxymorphone and the pH changes along the length of the gastrointestinal tract. Moreover, the chemistry of the components is believed to be similar to certain known muco-adhesive substances,

such as polycarbophil. Muco-adhesive properties are desirable for buccal delivery systems. Thus, the sustained release formulation can loosely interact with the mucin in the gastrointestinal tract and thereby provide another mode by which a constant rate of delivery of the oxymorphone is achieved.

The two phenomenon discussed above (buoyancy and muco-adhesive properties) are mechanisms by which the sustained release formulations of the invention can interact with the mucin and fluids of the gastrointestinal tract and provide a constant rate of delivery of the oxymorphone.

When measured by USP Procedure Drug Release USP 23 (incorporated by reference herein in its entirety), the sustained release formulations of the invention exhibit an in vitro dissolution rate of about 15% to about 50% by weight oxymorphone after 1 hour, about 45% to about 80% by weight oxymorphone after 4 hours, and at least about 80% by weight oxymorphone after 10 hours. The in vitro and in vivo release characteristics of the sustained release formulations of the invention may be modified using mixtures of one or more different water insoluble and/or water soluble compounds, using different plasticizers, varying the thickness of the sustained release film, including providing release-modifying compounds in the coating, and/or by providing passageways through the coating.

When administered orally to patients the sustained release formulations of the invention exhibit the following in vivo characteristics: (a) a peak plasma level of oxymorphone occurs within about 2 to about 6 hours after administration; (b) the duration of the oxymorphone analgesic effect is about 8 to about 24 hours; and (c) the relative oxymorphone bioavailability is about 0.5 to about 1.5 compared to an orally administered aqueous solution of oxymorphone.

While the compositions of the invention may be administered as the sole active pharmaceutical compound in the methods described herein, they can also be used in combination with one or more compounds which are known to be therapeutically effective against pain.

The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the compositions of the invention. The kits may further comprise other pharmaceutical compounds known in the art to be therapeutically effective against pain, and instructions for use.

EXAMPLES

The following examples are for purposes of illustration only and are not intended to limit the scope of the appended claims.

Examples 1 and 2

Two sustained release delivery systems were prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry was prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry was added to the dry blended mixture, and granulated for another 3 minutes. The granulation was then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation was then milled using 20 mesh screen. The relative quantities of the ingredients are listed in Table 1.

TABLE 1

Sustained Release Delivery System Excipient	Example 1 %	Example 2 %
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)[1]	(10)[1]	(20.0)[1]
Total	100.0	100.0

[1]Volatile, removed during processing

Examples 3 to 7

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the sustained release delivery system of Example 1. The quantities of ingredients per tablet are listed in Table 2.

TABLE 2

Component	Ex. 3 mg	Ex. 4 mg	Ex. 5 mg	Ex. 6 mg	Ex. 7 mg
Oxymorphone HCl, USP	5	10	20	40	80
Sustained release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
OPADRY ® (colored)	7.48	7.68	8.08	8.88	10.48
OPADRY ® (clear)	0.94	0.96	1.01	1.11	1.31

Examples 8 and 9

Two batches of tablets were prepared as described above for Examples 1-7, using the sustained release delivery system of Example 1. One batch was formulated to provide relatively fast sustained release, the other batch was formulated to provide relatively slow sustained release. Compositions of the tablets are shown in Table 3.

TABLE 3

Ingredients	Example 8 slow release mg/tablet	Example 9 fast release mg/tablet
Oxymorphone HCl, USP	20	20
Sustained Release Delivery System	360	160
Silicified Microcrystalline Cellulose, NF	20	20
Sodium stearyl fumarate, NF	4	2
Coating (color)	12.12	12.12
Total weight	416.12	214.12

The tables of Examples 8 and 9 were tested for in vitro release rate according to USP Procedure Drug Release USP 23. The results are shown in Table 4.

TABLE 4

Time (hr)	Example 8 slow release	Example 9 fast release
0.5	18.8%	21.3%
1	27.8%	32.3%

TABLE 4-continued

Time (hr)	Example 8 slow release	Example 9 fast release
2	40.5%	47.4%
3	50.2%	58.5%
4	58.1%	66.9%
5	64.7%	73.5%
6	70.2%	78.6%
8	79.0%	86.0%
10	85.3%	90.6%
12	89.8%	93.4%

Example 10

Clinical Study

A clinical study was conducted to (1) assess the relative bioavailability (rate and extent of absorption) of oxymorphone sustained release (20 mg) (fast release formulation of Example 9) compared to oral solution oxymorphone (10 mg) under fasted conditions, (2) to assess the relative bioavailability of oxymorphone sustained release (20 mg) compared to oral solution oxymorphone (10 mg) under fed conditions, (3) to assess the relative bioavailability of oxymorphone sustained release (20 mg) fed compared to oxymorphone sustained release (20 mg) fasted, (4) to assess the relative bioavailability of oral solution oxymorphone fed compared to oral solution oxymorphone fasted, and (5) to assess the relative safety and tolerability of sustained release oxymorphone (20 mg) under fed and fasted conditions.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment A and Treatment C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment B and Treatment D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment A and Treatment B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment C and Treatment D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments A and B were of oxymorphone sustained release 20 mg tablets. Subjects randomized to Treatment A received a single oral dose of one 20 mg oxymorphone sustained release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment B received a single oral dose of one 20 mg oxymorphone sustained release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments C and D were of oxymorphone HCl solutions, USP, 1.5 mg/ml injection 10 ml vials. Subjects randomized to Treatment C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment D received a single oral dose of 10 mg (6.7 mil) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds). The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

The subjects were screened within 14 days prior to study enrollment. The screening procedure included medical history, physical examination (height, weight, frame size, vital signs, and ECG), and clinical laboratory tests (hematology, serum chemistry, urinalysis, HIV antibody screen, Hepatitis B surface antigen screen, Hepatitis C antibody screen, and a screen for cannabinoids).

During the study, the subjects were to remain in an upright position (sitting or standing) for 4 hours after the study drug was administered. Water was restricted 2 hours predose to 2 hours postdose. During the study, the subjects were not allowed to engage in any strenuous activity.

Subjects reported to the clinic on the evening prior to each dosing. The subjects then observed a 10-hour overnight fast. On Day 1, subjects randomized to Treatment B and Treatment D received a high-fat breakfast within 30 minutes prior to dosing. A standardized meal schedule was then initiated with lunch 4 hours postdose, dinner 10 hours postdose, and a snack 13 hours postdose. On Day 2, a standardized meal was initiated with breakfast at 0815, lunch at 1200, and dinner at 1800. Subjects randomized to Treatment A and Treatment B received a snack at 2100 on Day 2.

Vital signs (sitting for 5 minutes and consisting of blood pressure, pulse, respiration, and temperature), and 12-lead ECG were assessed at the—13 hour point of each check-in period and at the completion of each period. A clinical laboratory evaluation (hematology, serum chemistry, urinalysis) and a brief physical examination were performed at the—13 hour of each check-in period and at the completion of the each period. Subjects were instructed to inform the study physician and/or nurses of any adverse events that occurred during the study.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment A and Treatment B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment C and Treatment D. A total of 80 blood samples (560 ml) per subject were drawn during the study for drug analysis. Plasma samples were separated by centrifugation, and then frozen at −70° C., and kept frozen until assayed.

An LC/MS/MS method was developed and validated for the determination of oxymorphone in human EDTA plasma. Samples were spiked with internal standard, d_3-oxymorphone, and placed on the RapidTrace® (Zymark Corporation, Hopkinton, Mass.) for automatic solid phase extraction. Extracts were dried under nitrogen and reconstituted with acetonitrile before injection onto an LC/MS/MS. The Perkin Elmer Sciex API III+, or equivalent, using a turbo ion spray interface was employed in this study. Positive ions were monitored in the MRM mode.

The pharmacokinetic parameters shown in Table 5 were computed from the plasma oxymorphone concentration-time data.

TABLE 5

AUC(0-t)	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.
AUC(0-inf)	Area under the drug concentration-time curve from time zero to infinity. AUC(0-inf) = AUC(0-t) + Ct/Kel, where Kel is the terminal elimination rate constant.
AUC(0-24)	Partial area under the drug concentration-time curve from time zero to 24 hours.
Cmax	Maximum observed drug concentration.
Tmax	Time of the observed maximum drug concentration.
Kel	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.
T1/2el	Half life, the time required for the concentration to decline by 50%, calculated as LN(2)/Kel

Terminal elimination rate constants were computed using linear regression of a minimum of three time points, at least two of which were consecutive. Kel values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus, T1/2el, AUC(0-inf), C1/F, MRT, and LN-transformed T1/2el, AUC(0-inf), and C1/F were also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding Tmax and Frel), and the LN-transformed parameters C_{max}, AUC (0-24), AUC(0-t), AUC(0-inf), C1/F, and T1/2el. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square). The following treatment comparisons of relative rate and extent of absorption were made: Treatment B versus Treatment A, Treatment A versus Treatment C (dose normalized to 20 mg). Treatment B versus Treatment D (dose normalized to 20 mg), and Treatment D versus Treatment C (dose normalized to 20 mg for both treatments). The 90% confidence intervals of the ratios of the treatment least squares parameter means were calculated. Tmax was analyzed using the Wilcoxon Signed Ranks test. Summary statistics were presented for Frel.

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

A total of 26 analytical runs were required to process the clinical samples from this study. Of these 26 analytical runs, 26 were acceptable for oxymorphone. Standard curves for the 26 analytical runs in EDTA plasma used in this study covered a range of 0.0500 to 20.000 mg/ml with a limit of quantitation of 0.0500 ng/ml for both compounds. Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 14.23% for oxymorphone.

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

The mean oxymorphone plasma concentration versus time curves for Treatments A, B, C, and D are presented in FIG. 1 (linear scale, without standard deviation).

Individual concentration versus time curves were characterized by multiple peaks which occurred in the initial 12-hour period following the dose. In addition, a small "bump" in plasma oxymorphone concentration was generally observed in the 24 to 48 hour post-dose period.

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment B versus Treatment A are summarized in Table 6.

TABLE 6

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments B and A

	Plasma Oxymorphone					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	1.7895	0.6531	1.1410	0.4537	125.4-191.0	158.2
Tmax(hr)	5.65	9.39	5.57	7.14		
Auc(0-24)(ng * hr/ml)	14.27	4.976	11.64	3.869	110.7-134.0	122.3
AUC(0-t)(ng * hr/ml)	19.89	6.408	17.71	8.471	100.2-123.6	111.9
AUC(0-inf) (ng * hr/ml)	21.29	6.559	19.29	5.028	105.3-133.9	119.6
T 1/2el(hr)	12.0	3.64	12.3	3.99	57.4-155.2	106.3

Treatment B = 1 × 20 mg oxymorphone sustained release Tablet, Fed: test
Treatment A = 1 × 20 mg oxymorphone sustained release Tablet, Fasted: reference

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment A versus Treatment C are summarized in Table 7.

TABLE 7

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment A		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	1.1410	0.4537	2.2635	1.0008	33.4-66.0	49.7
Tmax(hr)	5.57	7.14	0.978	1.14		
Auc(0-24)(ng * hr/ml)	11.64	3.869	12.39	4.116	82.8-104.6	93.7
AUC(0-I)(ng * hr/ml	17.71	8.471	14.53	4.909	107.7-136.3	122.0
AUC(0-inf) (ng * hr/ml)	19.29	5.028	18.70	6.618	80.2-108.4	94.3
T 1/2el(hr)	12.3	3.99	16.2	11.4	32.9-102.1	67.5

Treatment A = 1 x 20 mg oxymorphone sustained release Tablet, Fasted: test
Treatment C = 10 mg/6.7 ml oxymorphone HCI Oral Solution, Fasted: Dose Normalized to 20 ng: reference.

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment D versus Treatment C are summarized in Table 8.

TABLE 8

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment B		Treatment D			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	1.7895	0.6531	3.2733	1.3169	42.7-65.0	50.0
Tmax(hr)	5.65	9.39	1.11	0.768		
Auc(0-24)(ng * hr/ml)	14.27	4.976	17.30	5.259	74.4-90.1	82.2
AUC(0-t)(ng * hr/ml)	19.89	6.408	19.28	6.030	92.5-114.1	103.3
AUC(0-inf) (ng * hr/ml)	21.29	6.559	25.86	10.03	75.0-95.2	85.1
T 1/2el(hr)	12.0	3.64	20.6	19.3	31.9-86.1	59.0

Treatment B = 1 x 20 mg oxymorphone sustained release Tablet, Fed: test
Treatment D = 10 mg/6.7 ml oxymorphone HCI Oral Solution, Fed: Dose Normalized to 20 mg: reference.

The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistical comparisons for Treatment D versus Treatment C are summarized in Table 9.

TABLE 9

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment D		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax(ng/ml)	3.2733	1.3169	2.2635	1.0008	129.7-162.3	146.0
Tmax(hr)	1.11	0.768	0.978	1.14		
Auc(0-24)(ng * hr/ml)	17.30	5.259	12.39	4.116	128.5-150.3	139.4

TABLE 9-continued

Summary of the Pharmacokinetic Parameters of Plasma Oxymorphone for Treatments A and C

	Plasma Oxymorphone					
	Treatment D		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
AUC(0-t)(ng * hr/ml)	19.20	6.030	14.53	4.909	117.9-146.5	132.2
AUC(0-inf) (ng * hr/ml)	25.86	10.03	18.70	6.618	118.6-146.6	132.6
T 1/2el(hr)	20.6	19.3	16.2	11.4	87.3-155.9	121.6

Treatment D = 10 mg/6.7 ml oxymorphone HCl Oral Solution, Fed: Dose Normalized to 20 mg: test.
Treatment C = 10 mg/6.7 ml oxymorphone HCl Oral Solution, Fasted: Dose Normalized to 20 mg: reference.

The relative bioavailability calculations are summarized in Table 10.

TABLE 10

Mean (S.D.) Relative Oxymorphone Bioavailability Determined from AUC (0-inf) and AUC (0-24)

	Frel BA		Frel AC		Frel BD		Frel DC	
AUC(0-inf)	1.169	(0.2041)	1.040	(0.1874)	0.8863	(0.2569)	1.368	(0.4328)
AUC(0-24)	1.299	(0.4638)	(0.9598)	(0.2151)	0.8344	(0.100)	1.470	(0.3922)

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone sustained release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the sustained release formulation and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone Cmax, but less of an effect on oxymorphone AUC from oxymorphone sustained release tablets. Least Squares (LS) mean Cmax was 58% higher and LS mean AUC(0-t) and AUC(0-inf) were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from AUC (0-inf) since mean Frel was 1.17. Individual Frel values based on AUC (0-24) were similar (less than 20% different) to Frel values based on AUC (0-inf) for all but 2 subjects. Comparison of mean Frel from AUC (0-inf) to mean Frel from AUC (0-24) is misleading, because not all subjects had a value for AUC (0-inf). Mean Tmax values were similar (approximately 5.6 hours), and no significant different in Tmax was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean Cmax was 50% higher and LS mean AUC(0-t) and AUC(0-inf) were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from AUC(0-inf) since mean Frel was 1.37. Individual Frel values based on AUC(0-24) were similar (less than 20% different) to Frel values based on AUC(0-inf.) for all but 5 subjects. Comparison of mean Frel from AUC(0-inf) to mean Frel from AUC(0-24) is misleading because not all subjects had a value for AUC(0-inf). Mean Tmax (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone sustained release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean AUC(0-t) was 17% higher for oxymorphone sustained release, whereas LS mean AUC(0-inf) values were nearly equal (mean ratio=99%). However, AUC(0-t) is not the best parameter to evaluate bioavailability since the plasma concentrations were measured for 48 hours for the sustained release formulation versus 36 hours for the oral solution. Mean Frel values calculated from AUC(0-inf) and AUC(0-24), (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

There were differences in parameters reflecting rate of absorption. LS mean Cmax was 49% lower for oxymorphone sustained release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the sustained release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone sustained release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean AUC(0-inf) was 12% lower for oxymorphone sustained release. Mean Frel values calculated from AUC(0-inf) and AUC(0-24), (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. There were differences in parameters reflecting rate of absorption. LS mean Cmax was 46% lower

for oxymorphone sustained release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean Tmax was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the sustained release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability following administration of oxymorphone sustained release tablets. LS mean ratios were 97% for AUC(0-t) and 91% for Cmax (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from AUC(0-24), since mean Frel was 0.97. AUC(0-inf) was not a reliable measure for bioavailability since half-life could not be estimated accurately, and in many cases at all. Half-life estimates were not accurate because in the majority of subjects, the values for half-life were nearly as long or longer (up to 2.8 times longer) as the sampling period. Mean Tmax was later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone sustained release 20 mg tablets exhibited similar availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for AUC (0-t) was 104.5%. Mean Frel (0.83) calculated from AUC(0-24) also showed similar extent of oxymorphone availability between the two treatments. There were differences in parameters reflecting rate of absorption. LS mean Cmax was 57% lower for oxymorphone sustained release tablets compared to the dose-normalized oral solution. Mean Tmax was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the sustained release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability from oxymorphone sustained release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean AUC(0-t) was 14% higher for oxymorphone sustained release. Mean Frel (0.87) calculated from AUC (0-24) also indicated similar extent of availability between the treatments. There were differences in parameters reflecting rate of absorption. LS mean Cmax was 40% lower for oxymorphone sustained release tablets compared to the dose-normalized oral solution. Mean Tmax was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the sustained release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone sustained release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment, based on LN-transformed data. Tmax was unaffected by food; however, LS mean Cmax was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean Cmax and AUC values were increased approximately 50 and 30%, respectively. Tmax was unaffected by food. Under both fed and fasted conditions, oxymorphone sustained release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment.

Bioavailability following oxymorphone sustained release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean Cmax and AUC values for each treatment. Tmax was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, Cmax was decreased 35% in the presence of food. Tmax was unaffected by food. Under both fed and fasted conditions, oxymorphone sustained release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

Various modifications of the invention, in addition to those described herein, will be apparent to one skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim **1**, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim **1**, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulate sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

5. The oral sustained release formulation of claim **1**, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims **1-5**.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim **7**, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim **7**, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim **7**, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim **7**, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims **7-11**.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims **1-5**.

14. The solid dosage formulation of claim **13**, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of anyone of claims **7-11**.

16. The solid dosage formulation of claim **15**, wherein the solid dosage formulation is a tablet.

* * * * *

EXHIBIT 3

DUPLICATE

Wiley Rein LLP

1776 K STREET NW
WASHINGTON, DC 20006
PHONE 202.719.7000
FAX 202.719.7049

7925 JONES BRANCH DRIVE
McLEAN, VA 22102
PHONE 703.905.2800
FAX 703.905.2820

www.wileyrein.com

October 2, 2007

Benjamin B. Reed
202.719.7531
breed@wileyrein.com

BY HAND DELIVERY

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **TIME SENSITIVE PATENT INFORMATION**
NDA 21-610

To whom it may concern:

Enclosed please find a submission on behalf of Endo Pharmaceuticals, Inc. of supplemental patent information for NDA 21-610, Opana ER. United States Patent Number 7,276,250, claiming this product and two approved methods of use (claims 6 and 12) for this product, was issued on October 2, 2007.

Two copies of FDA Form 3542 (Patent Information Submitted Upon and After Approval of an NDA or Supplement) are enclosed in connection with this submission.

Please contact me at the number listed above if you have any questions.

Sincerely,

Benjamin B. Reed

Enclosures

cc: FDA Orange Book Staff
Guy Donatiello, Esq., Endo Pharmaceuticals, Inc.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-610

NAME OF APPLICANT / NDA HOLDER
Endo Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME
Opana ER

ACTIVE INGREDIENT(S)	STRENGTH(S)
Oxymorphone HCL	5 mg, 10 mg, 20 mg, 40 mg

DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
Tablet	06/22/2006

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7276250	10/02/2007	07/03/2022

d. Name of Patent Owner	Address *(of Patent Owner)*	
Penwest Pharmaceuticals Co.	39 Old Ridgebury Road; Suite #11	
	City/State: Danbury, CT	
	ZIP Code: 06810	FAX Number *(if available)*: (203) 794-1393
	Telephone Number: (203) 796-3700	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming an approved method of using the approved drug product. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?		☑ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6, 12	Does the patent claim referenced in **4.2** claim an approved method of use of the approved drug product?	☑ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.		

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)* Relief of moderate to severe pain

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information Below)*	Date Signed
Guy L. Donatiello	28 September 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Guy Donatiello, Esq	
Address 100 Endo Boulevard	City/State Chadds Ford, PA
ZIP Code 19317	Telephone Number (610) 558-9800
FAX Number *(if available)* (610) 558-9682	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

4.2) Identify by number each claim in the patent that claims the approved use(s) of the drug. Indicate whether or not each individual claim is a claim for the approved method(s) of use of the drug.

4.2a) Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. Each approved use claimed by the patent should be separately identified in this section.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

DUPLICATE

Wiley Rein LLP

1776 K STREET NW
WASHINGTON, DC 20006
PHONE 202.719.7000
FAX 202.719.7049

7925 JONES BRANCH DRIVE
McLEAN, VA 22102
PHONE 703.905.2800
FAX 703.905.2820

www.wileyrein.com

October 2, 2007

Benjamin B. Reed
202.719.7531
breed@wileyrein.com

BY HAND DELIVERY

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **TIME SENSITIVE PATENT INFORMATION**
NDA 21-610

To whom it may concern:

Enclosed please find a submission on behalf of Endo Pharmaceuticals, Inc. of supplemental patent information for NDA 21-610, Opana ER. United States Patent Number 7,276,250, claiming this product and two approved methods of use (claims 6 and 12) for this product, was issued on October 2, 2007.

Two copies of FDA Form 3542 (Patent Information Submitted Upon and After Approval of an NDA or Supplement) are enclosed in connection with this submission.

Please contact me at the number listed above if you have any questions.

Sincerely,

Benjamin B. Reed

Enclosures

cc: FDA Orange Book Staff
Guy Donatiello, Esq., Endo Pharmaceuticals, Inc.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-610

NAME OF APPLICANT / NDA HOLDER
Endo Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME
Opana ER

ACTIVE INGREDIENT(S)	STRENGTH(S)
Oxymorphone HCL	5 mg, 10 mg, 20 mg, 40 mg
DOSAGE FORM: Tablet	APPROVAL DATE OF NDA OR SUPPLEMENT: 06/22/2006

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7276250	10/02/2007	07/03/2022

d. Name of Patent Owner
Penwest Pharmaceuticals Co.

Address *(of Patent Owner)*
39 Old Ridgebury Road; Suite #11

City/State
Danbury, CT

ZIP Code
06810

FAX Number *(if available)*
(203) 794-1393

Telephone Number
(203) 796-3700

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming an approved method of using the approved drug product. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?	☑ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)*: 6, 12 — Does the patent claim referenced in **4.2** claim an approved method of use of the approved drug product?	☑ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)* Relief of moderate to severe pain

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

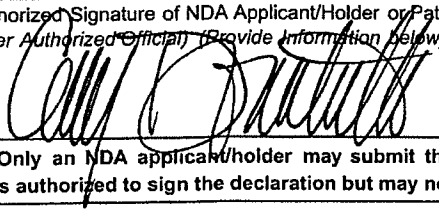
5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	28 September 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Guy Donatiello, Esq	
Address 100 Endo Boulevard	City/State Chadds Ford, PA
ZIP Code 19317	Telephone Number (610) 558-9800
FAX Number *(if available)* (610) 558-9682	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

4.2) Identify by number each claim in the patent that claims the approved use(s) of the drug. Indicate whether or not each individual claim is a claim for the approved method(s) of use of the drug.

4.2a) Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. Each approved use claimed by the patent should be separately identified in this section.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXHIBIT 4

30831 Huntwood Avenue Hayward, CA 94544
Phone (510) 476-2000 Fax (510) 476-2092

October 2, 2007

Via Federal Express

Endo Pharmaceuticals Inc.
100 Endo Blvd.
Chadds Ford, PA 19317

Tracking # 8613 5929 4551

Penwest Pharmaceuticals Co.
39 Old Ridgebury Rd., Suite 11
Danbury, CT 06810

Tracking # 8613 5929 4919

Re: Patent Certification Notice – U.S. Patent No. 7,276,250
Oxymorphone Hydrochloride Extended-release Tablets
ANDA 79-087

To Whom It May Concern:

This is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and (ii) (§§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax Laboratories, Inc. ("Impax"), a Delaware corporation with its principal place of business at 30831 Huntwood Avenue, Hayward, California, 94544, has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent No. 7,276,250.

A detailed statement of the factual and legal bases for Impax's position regarding this patent is provided herein. Impax reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patent is invalid, unenforceable, or not infringed.

An Offer of Confidential Access to Impax's ANDA 79-087, pursuant to 21 U.S.C. §355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Permission to use Federal Express for delivery of this notice and detailed statement was granted by Martin Shimer of the Office of Generic Drugs on September 24, 2007.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance

MCS/aks

Enclosures: Impax Laboratories, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patent No. 7,276,250 Is Invalid, Unenforceable Or Not Infringed

Impax Laboratories, Inc.'s Offer of Confidential Access to ANDA 79-087

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NO. 7,276,250 IS NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

This is the detailed statement of Impax Laboratories, Inc. ("Impax"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal basis for Impax's opinion that U.S. Patent No. 7,276,250 is invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, importation, use or sale of Impax's Oxymorphone HCl Extended Release 5 mg, 10 mg, 20 mg, and 40 mg tablets ("Impax Oxymorphone ER"), for which this detailed statement is submitted. Impax's factual and legal bases are set forth below.

I. Applicable Legal Standards

A U.S. patent gives the owner the right to preclude others from making, using or selling the invention defined by the claims of the patent in the United States and its territories for the term of the patent.[1] Those making, using or selling an invention defined by the claims of a patent are said to be directly infringing the claims of the patent. The patent statute also describes remedies for contributory infringement and inducement of infringement.[2] For there to be indirect infringement by one party, there must be direct infringement by another party. Furthermore, the act of filing an ANDA with patent invalidity or non-infringement certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) may create a cause of action for patent infringement.[3]

Evaluating infringement is a two-step process. First, the scope of the claims is determined, and second, the accused product or process is compared to the properly interpreted claims. The claims, properly construed as a matter of law by the court,[4] are the measure of the grant of the exclusive right to the patentee, and set out the metes and bounds of the invention.[5]

Claim construction may involve the use of both intrinsic and extrinsic evidence; however, the Federal Circuit in an *en banc* decision stressed the importance of giving the appropriate weight to such evidence.[6] In particular, the Federal Circuit has instructed trial courts that as a starting point, claim terms are to be given their ordinary and customary meaning as understood by one of ordinary skill in the art.[7] In determining the ordinary and customary meaning, the trial

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[1] 35 U.S.C. § 271(a).

[2] 35 U.S.C. § 271(b) & (c).

3 35 U.S.C. § 271(e)(2)(A).

[4] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995)(*en banc*), *aff'd*, 517 U.S. 370 (1996); *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

[5] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004).

[6] *Phillips v. AWH Corp. et al.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*).

[7] *Innova*, 381 F.3d at 1116; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

court must first consider the claim term not only in the context of the particular claim, but also in the context of the rest of the claims, the specification, and the prosecution history.[8]

Once the language of the claims is properly interpreted, the claims must be "read on" the accused structure to determine whether each of the limitations recited in the claim is present.[9] Under the "all-elements" rule, a claim is not infringed unless each element of the claim, or a substantial equivalent of that element, is found in the accused device[10] When any limitation recited in a claim is not met, literal infringement is avoided.[11]

The absence of literal infringement does not necessarily mean that a process or device does not infringe a patent. The judicially created "doctrine of equivalents" allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes.[12] Thus, even though the language of a claim cannot be read literally upon a process or device, a claim can be infringed if the process or device "performs substantially the same function in substantially the same way to obtain the same result."[13] What constitutes "equivalency" must be determined against the context of the patent, the prior art, and the particular circumstances of the case.

A patent and each of its issued claims is presumed to be valid.[14] Proof of invalidity of a patent or its claims is a complete defense to a charge of infringement of the claims of that patent. The claims of a patent can be found to be invalid under 35 U.S.C. §103 because they are obvious in light of the prior art. With respect to patent claim invalidity, "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

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[8] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005); *Vitronics*, 90 F.3d at 1582-83 (Fed. Cir. 1996).

[9] *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989).

[10] *Pennwalt Corp. v. Durand-Wayland Co.*, 833 F.2d 931, 935, (Fed. Cir. 1987); *Corning Glass Works*, 868 F.2d at 1259.

[11] *Lemelson v. United States*, 752 F.2d 1538 (Fed. Cir. 1985). See also, *Cooper Cameron Corp. v. Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317 (Fed. Cir. 2002).

[12] *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. et al.*, 535 U.S. 722, 723 (2002).

[13] *Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). See also *Jonnson v. Stanley Works*, 711 F. Supp. 1395, 1407 (N.D. Ohio, 1989), *aff'd*, 903 F.2d 812 (Fed. Cir. 1990); *Fantasy Sports Properties, Inc. v. SportsLine.com, Inc.*, 287 F.3d 1108 (Fed. Cir. 2002).

[14] 35 U.S.C. § 282.

a person having ordinary skill in the art to which said subject matter pertains."[15] The "combination of familiar elements according to known methods" is likely be obvious when it yields predictable results, and common sense, not a "formalistic conception of the words teaching, suggestion, and motivation" should guide obviousness analysis.[16] Factors to be considered in determining obviousness include the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the art, and secondary considerations.[17]

A patent application must describe how to make and use the invention in such full, clear, concise and exact terms as to enable any person of ordinary skill in the art to which it pertains to make and use the same.[18] For a claim to be enabled, the disclosure must be sufficiently described as to enable one of ordinary skill in the art to practice the invention without undue experimentation. A patent can be enabled even if it requires some experimentation to practice the invention: what is proscribed is undue experimentation.

Furthermore, the specification must be enabled at the time of filing the application, and a later filed publication cannot supplement an insufficient disclosure to render it enabling.[19] Later filed publications can be considered as evidence of the level of ordinary skill in the art at the time of filing the application, reinforcing the standard that the issue is whether one skilled in the art would have believed the application to be enabled at the time of filing. *In re Wands* set out 8 factors to be considered for enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill in the art, (5) the level of predictability in the art, (6) the amount of direction provided in the application, (7) the existence of working examples in the specification, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.[20]

In order for a claim to be patentable, it also must meet the written description requirements of 35 U.S.C. § 112, Paragraph 1. The goals of the written description requirement are to (1) convey to the public what was invented, (2) put the public in possession of what the applicant claims as the invention, and (3) prevent an applicant from claiming subject matter that

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[15] 35 U.S.C. § 103(a).

[16] *KSR Int'l Co. v. Teleflex Inc., et al.*, 127 S.Ct. 1727, 1739-41 (2007).

[17] *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

[18] *See* 35 U.S.C. §112, 1st paragraph.

[19] *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

[20] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

was not described in the specification as filed. As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing."[21] Possession of the invention is shown by describing the invention with specificity such as by words, structures, figures, diagrams, and formulas.[22]

The second paragraph of §112 requires the specification of a patent to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[23] To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim.[24] Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [the Federal Circuit Court has] asked is that the claims be amenable to construction, however difficult that task may be."[25]

Furthermore, a patent may be rendered unenforceable for inequitable conduct. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith, and honesty.'"[26] "To hold a patent unenforceable due to inequitable conduct, there must be clear and convincing evidence that the applicant (1) made an affirmative misrepresentation or material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]."[27] Intent need not, and rarely can, be proven by direct evidence.[28] "[I]n the absence of a credible explanation, intent to deceive *is generally inferred* from the facts and circumstances surrounding a knowing failure to disclose material information."[29] Further, the Federal Circuit recently "made it clear that 'a patentee facing a high level of materiality and clear proof that it knew or should have known of that

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[21] *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1259 (Fed. Cir. 2004).

[22] Revised Interim Written Description Guidelines, available at <http://www.uspto.gov/web/menu/written.pdf>.

[23] *See* 35 U.S.C. § 112, 2nd paragraph.

[24] *Miles Lab. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[25] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[26] *Ferring B.V. v. Barr Labs*, 437 F.3d 1181, 1186-87 (Fed. Cir. 2006) (quoting *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005)).

[27] *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007).

[28] *Merck & Co., Inc. v. Danbury Pharmacal, Inc.* 873 F.2d 1418, 1422 (Fed. Cir. 1989).

[29] *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead.'"[30]

II. U.S. Patent No. 7,276,250

U.S. Patent No. 7,276,250 (the "'250 patent") was filed on July 3, 2002 and issued on October 2, 2007. The '250 patent claims priority to U.S. Provisional Application No. 60/329,352, filed October 15, 2001, U.S. Provisional Application No. 60/329,426, filed October 15, 2001, and U.S. Provisional Application No. 60/303,357, filed July 6, 2001. The '250 patent is assigned to Penwest Pharmaceuticals Company of Patterson, New York.

A. The Claims of the '250 patent

There are sixteen claims issued in the '250 patent, which read as follows:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim 1, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim 1, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

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[30] *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997)).

5. The oral sustained release formulation of claim 1, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 1-5.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim 7, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim 7, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim 7, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim 7, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 7-11.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 1-5.

14. The solid dosage formulation of claim 13, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 7-11.

16. The solid dosage formulation of claim 15, wherein the solid dosage formulation is a tablet.

B. No Infringement of the Claims of the '250 patent

The '250 patent contains only 3 independent claims. Each of the independent claims 1, 4, and 7 of the '250 patent contains the specific limitation that the composition must include dextrose, among other ingredients. Specifically, the compositions of claims 1 and 7 require "about 20% to about 55% by weight dextrose." The composition of claim 4 requires "about 35% dextrose." Because each remaining claim contains the limitations of the independent claim from it depends, all of the claims in the '250 patent require the presence of dextrose, in the respective amounts claimed, for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claims of the '250 patent because Impax Oxymorphone ER does not contain dextrose in the claimed amounts. Furthermore, Impax's Oxymorphone ER would not infringe any claim under the doctrine of equivalents. Patentees are entitled to no range of equivalents around the "about 20% to about 55% by weight dextrose" and "about 35% dextrose" claim limitations. During prosecution, in order to obtain allowance, claims requiring "at least one pharmaceutical diluent" were cancelled in favor of the narrower claims specifying dextrose in the amounts listed above. Applicants are estopped from arguing equivalents to these claim limitations as no exceptions to the complete bar to the doctrine of equivalents apply in this case. Therefore, the Impax Oxymorphone ER does not contain any equivalent to the amounts of dextrose claimed in the '250 patent.

C. Conclusion

For the reasons stated above, none of the claims of U.S. Patent No. 7,276,250 are infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER. Impax reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable or not infringed.

ABBREVIATED NEW DRUG APPLICATION 79-087
OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Impax Laboratories, Inc. ("Impax") has provided notice to Endo Pharmaceuticals Inc. (hereinafter "Recipient") that Impax submitted to the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application No. 79-087 for Impax's Oxymorphone Hydrochloride Extended-release Tablets, (hereinafter referred to in whole or in part as the "ANDA"), containing a Paragraph IV certification with respect to U.S. Patent No. 7,276,250 (the "Listed Patent") which is listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations;" and

WHEREAS this document constitutes Impax's Offer of Confidential Access to that ANDA pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

WHEREAS Impax offers to provide Recipient confidential access to the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

WHEREAS this document accompanies Impax's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patent;

NOW, THEREFORE, Impax makes this offer:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions recited in clause 2 below, Impax hereby provides Recipient this Offer of Confidential Access for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to the Listed Patent.

2. The right of confidential access offered herein is subject to the following restrictions as to persons entitled to access, and the use and disposition of any information accessed, pursuant to this Offer of Confidential Access:

   A. **Persons Entitled to Access**: Persons entitled to access (hereinafter referred to as "Authorized Evaluators") under this Offer of Confidential Access are restricted to

outside counsel engaged by Recipient to represent Recipient and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that:

i. Such outside counsel has been identified to Impax in writing;

ii. Such outside counsel is not involved in patent prosecution matters for Recipient;

iii. Within five (5) business days of receiving such written identification, Impax has not objected, in writing, to provision of confidential access to the identified outside counsel.

B. **Materials Accessible by Authorized Evaluators**: A copy of the ANDA, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. **Use of the ANDA and Information in the ANDA**:

i. Subject to paragraph 2(D)(ii)(a), use of the ANDA, and all information contained therein or derived therefrom, and all notes, analyses, studies, or documents prepared by Authorized Evaluators to the extent they reflect the contents of the ANDA furnished herein, is for the sole and limited purpose of evaluating possible infringement of the Listed Patent and for no other purpose.

ii. Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information in the ANDA, to any person other than an Authorized Evaluator.

iii. Notwithstanding the provisions of subparagraphs 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Recipient on whether or not to assert the Listed Patent, provided, however, that the information in the ANDA is not thereby disclosed.

D. **Disposition of the Information in the ANDA:**

i. If Recipient does not assert the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Authorized Evaluators shall, and Recipient shall direct and ensure that Authorized Evaluators, within thirty (30) days after the expiration of the 45-day period, destroy or send to Impax the portions of the ANDA provided, and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, and Recipient or Authorized Evaluators shall notify Impax that this has been done.

ii. Recipient agrees that if Recipient asserts the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement which this offer accompanies:

a. While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Impax. Until such a protective order is entered, subsection 2(C)(ii) above continues to apply.

b. Recipient shall direct and ensure that Authorized Evaluators destroy the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, within thirty (30) days after the final determination of the action brought against Impax.

iii. Notwithstanding the provisions of subparagraphs 2(D)(i) and 2(D)(ii) above, the Authorized Evaluators identified in subparagraph 2(A) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document prepared by Authorized Evaluators to the extent that they reflect information in the ANDA.

E. **Accidental Disclosure:** Should information from the ANDA be disclosed, inadvertently or otherwise, Recipient shall, at Recipient's earliest opportunity, contact Impax and identify:

i. What has been disclosed;

ii. The individuals to whom such information has been disclosed; and

iii. Steps taken by Recipient and Authorized Evaluators to ensure the information in the ANDA continues to be treated pursuant to the terms of this agreement and is not further disseminated.

3. Recipient and Authorized Evaluators recognize that violation of any provision of this Offer of Confidential Access will cause irreparable injury to Impax, and that an adequate legal remedy does not exist. Impax, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipient and Authorized Evaluators from violating the terms of this Offer of Confidential Access. It is further agreed that in such an action Impax is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer of Confidential Access be found by a court of competent jurisdiction to be illegal, unconstitutional and/or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the information in the ANDA, except for the purpose expressly stated herein.

6. This Agreement shall be governed by the laws of the State of California, without giving effect to its conflicts of law or choice of law principles.

7. Each of Recipient, Authorized Evaluators and Impax, irrevocably submit to and accept, generally and unconditionally, the exclusive personal jurisdiction of the courts of the State of California, and of the U.S. District Court for the Northern District of California, waives its right to assert any objection or defense based on venue or *forum non conveniens* and agrees to be bound by any judgment rendered thereby arising under or in respect of this Agreement.

8. When accepted by the parties hereto, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

9. An Authorized Evaluator may request access to the ANDA by executing one copy of this Confidential Access Agreement where indicated and returning the executed copy to Impax within the 45-day period. Thereupon, the terms contained in this document shall be considered an enforceable contract between Impax and the Recipient.

Impax Laboratories, Inc.

Charles Hildenbrand, Sr. Vice-President of Operations

Date: 27 Sept, 2007

Recipient
By its authorized agent(s):

Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____, 2007

EXHIBIT 5

Press Release

IMPAX Comments on Status of ANDA for Generic Opana(R) ER

HAYWARD, Calif., Oct 04, 2007 (BUSINESS WIRE) -- IMPAX Laboratories, Inc. (OTC:IPXL) today confirmed reports that it has provided notice to Endo Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. that it has submitted an Abbreviated New Drug Application (ANDA) for oxymorphone hydrochloride extended-release tablets CII, generic of Opana (R) ER, to the U.S. Food and Drug Administration (FDA). IMPAX's ANDA, as amended, contains a Paragraph IV certification stating that the Company believes its product does not infringe US Patent No. 7,276,250, or that the patent is invalid or unenforceable. Following an acceptance for filing by the FDA the Company was informed by the agency that it has rescinded its initial acceptance. IMPAX believes that the rescission is inappropriate and is working with the FDA to correct any deficiencies of the ANDA.

Endo Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. manufacture and market Opana ER for the treatment of moderate to severe pain. According to Wolters Kluwer Health, U.S. sales of Opana ER tablets were approximately $42.9 million in the 12 months ended August 31, 2007.

About IMPAX Laboratories, Inc.

IMPAX Laboratories, Inc. is a technology based specialty pharmaceutical company applying its formulation expertise and drug delivery technology to the development of controlled-release and specialty generics in addition to the development of branded products. IMPAX markets its generic products through its Global Pharmaceuticals division and markets its branded products through the IMPAX Pharmaceuticals division. Additionally, where strategically appropriate, IMPAX has developed marketing partnerships to fully leverage its technology platform. IMPAX Laboratories is headquartered in Hayward, California, and has a full range of capabilities in its Hayward and Philadelphia facilities. For more information, please visit the Company's Web site at: www.impaxlabs.com.

"Safe Harbor" statement under the Private Securities Litigation Reform Act of 1995:

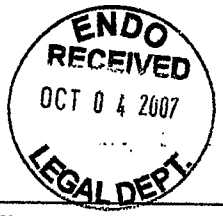
To the extent any statements made in this news release contain information that is not historical, these statements are forward-looking in nature and express the beliefs and expectations of management. Such statements are based on current expectations and involve a number of known and unknown risks and uncertainties that could cause IMPAX's future results, performance or achievements to differ significantly from the results, performance or achievements expressed or implied by such forward-looking statements. Such risks and uncertainties include, but are not limited to, possible adverse effects resulting from the delisting of and suspension of trading in IMPAX's stock, the SEC proceeding to determine whether to suspend or revoke the registration of IMPAX's securities under section 12 of the Securities Exchange Act, IMPAX's delay in filing its 2004 Form 10-K, its Form 10-Q for each of the first three quarters of 2005 and 2006, its Form 10-K for 2005 and 2006, and its Form 10-Q for the first quarter of 2007, the actual time that will be required to complete the filing of IMPAX's delinquent periodic reports, IMPAX's ability to obtain sufficient capital to fund its operations, the difficulty of predicting FDA filings and approvals, consumer acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, IMPAX's ability to successfully develop and commercialize pharmaceutical products, IMPAX's reliance on key strategic alliances, the uncertainty of patent litigation, the availability of raw materials, the regulatory environment, dependence on patent and other protection for innovative products, exposure to product liability claims, fluctuations in operating results and other risks detailed from time to time in IMPAX's filings with the Securities and Exchange Commission. Forward-looking statements speak only as to the date on which they are made, and IMPAX undertakes no obligation to update publicly or revise any forward-looking statement, regardless of whether new information becomes available, future developments occur or otherwise.

SOURCE: IMPAX Laboratories, Inc.

Company Contacts:
IMPAX Laboratories, Inc.
Larry Hsu, Ph.D. President & CEO
510-476-2000, Ext. 1111

Arthur A. Koch, Jr. CFO
215-933-0351
www.impaxlabs.com
or
Investor Relations Contacts:
Lippert/Heilshorn & Associates, Inc.
Kim Sutton Golodetz, 212-838-3777
kgolodetz@lhai.com
Bruce Voss, 310-691-7100
bvoss@lhai.com
www.lhai.com

EXHIBIT 6



30831 Huntwood Avenue Hayward, CA 94544
Phone (510) 476-2000 Fax (510) 476-2092

October 3, 2007

Via Federal Express

Endo Pharmaceuticals Inc.
100 Endo Blvd.
Chadds Ford, PA 19317

Tracking # 8613 5929 4920

Penwest Pharmaceuticals Co.
39 Old Ridgebury Rd., Suite 11
Danbury, CT 06810

Tracking # 8613 5929 4930

Re: Patent Certification Notice – U.S. Patent No. 7,276,250
Oxymorphone Hydrochloride Extended-release Tablets
ANDA 79-087

To Whom It May Concern:

This is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and (ii) (§§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax Laboratories, Inc. ("Impax"), a Delaware corporation with its principal place of business at 30831 Huntwood Avenue, Hayward, California, 94544, has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent No. 7,276,250.

A detailed statement of the factual and legal bases for Impax's position regarding this patent is provided herein. Impax reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patent is invalid, unenforceable, or not infringed.

An Offer of Confidential Access to Impax's ANDA 79-087, pursuant to 21 U.S.C. §355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Permission to use Federal Express for delivery of this notice and detailed statement was granted by Martin Shimer of the Office of Generic Drugs on September 24, 2007.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance

MCS/aks

Enclosures: Impax Laboratories, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patent No. 7,276,250 Is Invalid, Unenforceable Or Not Infringed

Impax Laboratories, Inc.'s Offer of Confidential Access to ANDA 79-087

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NO. 7,276,250 IS NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

This is the detailed statement of Impax Laboratories, Inc. ("Impax"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal basis for Impax's opinion that U.S. Patent No. 7,276,250 is invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, importation, use or sale of Impax's Oxymorphone HCl Extended Release 5 mg, 10 mg, 20 mg, and 40 mg tablets ("Impax Oxymorphone ER"), for which this detailed statement is submitted. Impax's factual and legal bases are set forth below.

I. Applicable Legal Standards

A U.S. patent gives the owner the right to preclude others from making, using or selling the invention defined by the claims of the patent in the United States and its territories for the term of the patent.[1] Those making, using or selling an invention defined by the claims of a patent are said to be directly infringing the claims of the patent. The patent statute also describes remedies for contributory infringement and inducement of infringement.[2] For there to be indirect infringement by one party, there must be direct infringement by another party. Furthermore, the act of filing an ANDA with patent invalidity or non-infringement certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) may create a cause of action for patent infringement.[3]

Evaluating infringement is a two-step process. First, the scope of the claims is determined, and second, the accused product or process is compared to the properly interpreted claims. The claims, properly construed as a matter of law by the court,[4] are the measure of the grant of the exclusive right to the patentee, and set out the metes and bounds of the invention.[5]

Claim construction may involve the use of both intrinsic and extrinsic evidence; however, the Federal Circuit in an *en banc* decision stressed the importance of giving the appropriate weight to such evidence.[6] In particular, the Federal Circuit has instructed trial courts that as a starting point, claim terms are to be given their ordinary and customary meaning as understood by one of ordinary skill in the art.[7] In determining the ordinary and customary meaning, the trial

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[1] 35 U.S.C. § 271(a).

[2] 35 U.S.C. § 271(b) & (c).

[3] 35 U.S.C. § 271(e)(2)(A).

[4] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995)(*en banc*), *aff'd*, 517 U.S. 370 (1996); *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

[5] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004).

[6] *Phillips v. AWH Corp. et al.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*).

[7] *Innova*, 381 F.3d at 1116; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

court must first consider the claim term not only in the context of the particular claim, but also in the context of the rest of the claims, the specification, and the prosecution history.[8]

Once the language of the claims is properly interpreted, the claims must be "read on" the accused structure to determine whether each of the limitations recited in the claim is present.[9] Under the "all-elements" rule, a claim is not infringed unless each element of the claim, or a substantial equivalent of that element, is found in the accused device[10] When any limitation recited in a claim is not met, literal infringement is avoided.[11]

The absence of literal infringement does not necessarily mean that a process or device does not infringe a patent. The judicially created "doctrine of equivalents" allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes.[12] Thus, even though the language of a claim cannot be read literally upon a process or device, a claim can be infringed if the process or device "performs substantially the same function in substantially the same way to obtain the same result."[13] What constitutes "equivalency" must be determined against the context of the patent, the prior art, and the particular circumstances of the case.

A patent and each of its issued claims is presumed to be valid.[14] Proof of invalidity of a patent or its claims is a complete defense to a charge of infringement of the claims of that patent. The claims of a patent can be found to be invalid under 35 U.S.C. §103 because they are obvious in light of the prior art. With respect to patent claim invalidity, "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

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[8] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005); *Vitronics*, 90 F.3d at 1582-83 (Fed. Cir. 1996).

[9] *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989).

[10] *Pennwalt Corp. v. Durand-Wayland Co.*, 833 F.2d 931, 935, (Fed. Cir. 1987); *Corning Glass Works*, 868 F.2d at 1259.

[11] *Lemelson v. United States*, 752 F.2d 1538 (Fed. Cir. 1985). See also, *Cooper Cameron Corp. v. Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317 (Fed. Cir. 2002).

[12] *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. et al.*, 535 U.S. 722, 723 (2002).

[13] *Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). See also *Jonnson v. Stanley Works*, 711 F. Supp. 1395, 1407 (N.D. Ohio, 1989), *aff'd*, 903 F.2d 812 (Fed. Cir. 1990); *Fantasy Sports Properties, Inc. v. SportsLine.com, Inc.*, 287 F.3d 1108 (Fed. Cir. 2002).

[14] 35 U.S.C. § 282.

a person having ordinary skill in the art to which said subject matter pertains."[15] The "combination of familiar elements according to known methods" is likely be obvious when it yields predictable results, and common sense, not a "formalistic conception of the words teaching, suggestion, and motivation" should guide obviousness analysis.[16] Factors to be considered in determining obviousness include the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the art, and secondary considerations.[17]

A patent application must describe how to make and use the invention in such full, clear, concise and exact terms as to enable any person of ordinary skill in the art to which it pertains to make and use the same.[18] For a claim to be enabled, the disclosure must be sufficiently described as to enable one of ordinary skill in the art to practice the invention without undue experimentation. A patent can be enabled even if it requires some experimentation to practice the invention: what is proscribed is undue experimentation.

Furthermore, the specification must be enabled at the time of filing the application, and a later filed publication cannot supplement an insufficient disclosure to render it enabling.[19] Later filed publications can be considered as evidence of the level of ordinary skill in the art at the time of filing the application, reinforcing the standard that the issue is whether one skilled in the art would have believed the application to be enabled at the time of filing. *In re Wands* set out 8 factors to be considered for enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill in the art, (5) the level of predictability in the art, (6) the amount of direction provided in the application, (7) the existence of working examples in the specification, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.[20]

In order for a claim to be patentable, it also must meet the written description requirements of 35 U.S.C. § 112, Paragraph 1. The goals of the written description requirement are to (1) convey to the public what was invented, (2) put the public in possession of what the applicant claims as the invention, and (3) prevent an applicant from claiming subject matter that

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[15] 35 U.S.C. § 103(a).

[16] *KSR Int'l Co. v. Teleflex Inc., et al.*, 127 S.Ct. 1727, 1739-41 (2007).

[17] *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

[18] *See* 35 U.S.C. §112, 1st paragraph.

[19] *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

[20] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

was not described in the specification as filed. As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing."[21] Possession of the invention is shown by describing the invention with specificity such as by words, structures, figures, diagrams, and formulas.[22]

The second paragraph of §112 requires the specification of a patent to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[23] To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim.[24] Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [the Federal Circuit Court has] asked is that the claims be amenable to construction, however difficult that task may be."[25]

Furthermore, a patent may be rendered unenforceable for inequitable conduct. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith, and honesty.'"[26] "To hold a patent unenforceable due to inequitable conduct, there must be clear and convincing evidence that the applicant (1) made an affirmative misrepresentation or material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]."[27] Intent need not, and rarely can, be proven by direct evidence.[28] "[I]n the absence of a credible explanation, intent to deceive *is generally inferred* from the facts and circumstances surrounding a knowing failure to disclose material information."[29] Further, the Federal Circuit recently "made it clear that 'a patentee facing a high level of materiality and clear proof that it knew or should have known of that

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[21] *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1259 (Fed. Cir. 2004).

[22] Revised Interim Written Description Guidelines, available at <http://www.uspto.gov/web/menu/written.pdf>.

[23] *See* 35 U.S.C. § 112, 2nd paragraph.

[24] *Miles Lab. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[25] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[26] *Ferring B.V. v. Barr Labs*, 437 F.3d 1181, 1186-87 (Fed. Cir. 2006) (quoting *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005)).

[27] *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007).

[28] *Merck & Co., Inc. v. Danbury Pharmacal, Inc.* 873 F.2d 1418, 1422 (Fed. Cir. 1989).

[29] *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead.'"[30]

II. U.S. Patent No. 7,276,250

U.S. Patent No. 7,276,250 (the "'250 patent") was filed on July 3, 2002 and issued on October 2, 2007. The '250 patent claims priority to U.S. Provisional Application No. 60/329,352, filed October 15, 2001, U.S. Provisional Application No. 60/329,426, filed October 15, 2001, and U.S. Provisional Application No. 60/303,357, filed July 6, 2001. The '250 patent is assigned to Penwest Pharmaceuticals Company of Patterson, New York.

A. The Claims of the '250 patent

There are sixteen claims issued in the '250 patent, which read as follows:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim 1, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim 1, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

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[30] *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997)).

5. The oral sustained release formulation of claim 1, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 1-5.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim 7, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim 7, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim 7, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim 7, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 7-11.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 1-5.

14. The solid dosage formulation of claim 13, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 7-11.

16. The solid dosage formulation of claim 15, wherein the solid dosage formulation is a tablet.

B. No Infringement of the Claims of the '250 patent

The '250 patent contains only 3 independent claims. Each of the independent claims 1, 4, and 7 of the '250 patent contains the specific limitation that the composition must include dextrose, among other ingredients. Specifically, the compositions of claims 1 and 7 require "about 20% to about 55% by weight dextrose." The composition of claim 4 requires "about 35% dextrose." Because each remaining claim contains the limitations of the independent claim from it depends, all of the claims in the '250 patent require the presence of dextrose, in the respective amounts claimed, for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claims of the '250 patent because Impax Oxymorphone ER does not contain dextrose in the claimed amounts. Furthermore, Impax's Oxymorphone ER would not infringe any claim under the doctrine of equivalents. Patentees are entitled to no range of equivalents around the "about 20% to about 55% by weight dextrose" and "about 35% dextrose" claim limitations. During prosecution, in order to obtain allowance, claims requiring "at least one pharmaceutical diluent" were cancelled in favor of the narrower claims specifying dextrose in the amounts listed above. Applicants are estopped from arguing equivalents to these claim limitations as no exceptions to the complete bar to the doctrine of equivalents apply in this case. Therefore, the Impax Oxymorphone ER does not contain any equivalent to the amounts of dextrose claimed in the '250 patent.

C. Conclusion

For the reasons stated above, none of the claims of U.S. Patent No. 7,276,250 are infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER. Impax reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable or not infringed.

ABBREVIATED NEW DRUG APPLICATION 79-087
OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Impax Laboratories, Inc. ("Impax") has provided notice to Endo Pharmaceuticals Inc. (hereinafter "Recipient") that Impax submitted to the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application No. 79-087 for Impax's Oxymorphone Hydrochloride Extended-release Tablets, (hereinafter referred to in whole or in part as the "ANDA"), containing a Paragraph IV certification with respect to U.S. Patent No. 7,276,250 (the "Listed Patent") which is listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations;" and

WHEREAS this document constitutes Impax's Offer of Confidential Access to that ANDA pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

WHEREAS Impax offers to provide Recipient confidential access to the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

WHEREAS this document accompanies Impax's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patent;

NOW, THEREFORE, Impax makes this offer:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions recited in clause 2 below, Impax hereby provides Recipient this Offer of Confidential Access for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to the Listed Patent.

2. The right of confidential access offered herein is subject to the following restrictions as to persons entitled to access, and the use and disposition of any information accessed, pursuant to this Offer of Confidential Access:

   A. **Persons Entitled to Access**: Persons entitled to access (hereinafter referred to as "Authorized Evaluators") under this Offer of Confidential Access are restricted to

outside counsel engaged by Recipient to represent Recipient and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that:

i. Such outside counsel has been identified to Impax in writing;

ii. Such outside counsel is not involved in patent prosecution matters for Recipient;

iii. Within five (5) business days of receiving such written identification, Impax has not objected, in writing, to provision of confidential access to the identified outside counsel.

B. **Materials Accessible by Authorized Evaluators**: A copy of the ANDA, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. **Use of the ANDA and Information in the ANDA**:

i. Subject to paragraph 2(D)(ii)(a), use of the ANDA, and all information contained therein or derived therefrom, and all notes, analyses, studies, or documents prepared by Authorized Evaluators to the extent they reflect the contents of the ANDA furnished herein, is for the sole and limited purpose of evaluating possible infringement of the Listed Patent and for no other purpose.

ii. Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information in the ANDA, to any person other than an Authorized Evaluator.

iii. Notwithstanding the provisions of subparagraphs 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Recipient on whether or not to assert the Listed Patent, provided, however, that the information in the ANDA is not thereby disclosed.

D. **Disposition of the Information in the ANDA:**

i. If Recipient does not assert the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Authorized Evaluators shall, and Recipient shall direct and ensure that Authorized Evaluators, within thirty (30) days after the expiration of the 45-day period, destroy or send to Impax the portions of the ANDA provided, and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, and Recipient or Authorized Evaluators shall notify Impax that this has been done.

ii. Recipient agrees that if Recipient asserts the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement which this offer accompanies:

a. While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Impax. Until such a protective order is entered, subsection 2(C)(ii) above continues to apply.

b. Recipient shall direct and ensure that Authorized Evaluators destroy the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, within thirty (30) days after the final determination of the action brought against Impax.

iii. Notwithstanding the provisions of subparagraphs 2(D)(i) and 2(D)(ii) above, the Authorized Evaluators identified in subparagraph 2(A) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document prepared by Authorized Evaluators to the extent that they reflect information in the ANDA.

E. **Accidental Disclosure:** Should information from the ANDA be disclosed, inadvertently or otherwise, Recipient shall, at Recipient's earliest opportunity, contact Impax and identify:

i. What has been disclosed;

ii. The individuals to whom such information has been disclosed; and

iii. Steps taken by Recipient and Authorized Evaluators to ensure the information in the ANDA continues to be treated pursuant to the terms of this agreement and is not further disseminated.

3. Recipient and Authorized Evaluators recognize that violation of any provision of this Offer of Confidential Access will cause irreparable injury to Impax, and that an adequate legal remedy does not exist. Impax, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipient and Authorized Evaluators from violating the terms of this Offer of Confidential Access. It is further agreed that in such an action Impax is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer of Confidential Access be found by a court of competent jurisdiction to be illegal, unconstitutional and/or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the information in the ANDA, except for the purpose expressly stated herein.

6. This Agreement shall be governed by the laws of the State of California, without giving effect to its conflicts of law or choice of law principles.

7. Each of Recipient, Authorized Evaluators and Impax, irrevocably submit to and accept, generally and unconditionally, the exclusive personal jurisdiction of the courts of the State of California, and of the U.S. District Court for the Northern District of California, waives its right to assert any objection or defense based on venue or *forum non conveniens* and agrees to be bound by any judgment rendered thereby arising under or in respect of this Agreement.

8. When accepted by the parties hereto, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

9. An Authorized Evaluator may request access to the ANDA by executing one copy of this Confidential Access Agreement where indicated and returning the executed copy to Impax within the 45-day period. Thereupon, the terms contained in this document shall be considered an enforceable contract between Impax and the Recipient.

Impax Laboratories, Inc.

Charles Hildenbrand, Sr. Vice-President of Operations

Date: 27 Sept, 2007

Recipient
By its authorized agent(s):

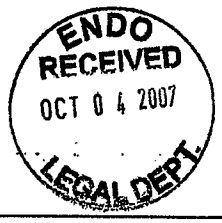
Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____, 2007



30831 Huntwood Avenue Hayward, CA 94544
Phone (510) 476-2000 Fax (510) 476-2092

October 4, 2007

Via Federal Express

Endo Pharmaceuticals Inc.
100 Endo Blvd.
Chadds Ford, PA 19317

Tracking # 8613 5929 4941

Penwest Pharmaceuticals Co.
39 Old Ridgebury Rd., Suite 11
Danbury, CT 06810

Tracking # 8613 5929 4952

Re: Patent Certification Notice – U.S. Patent No. 7,276,250
Oxymorphone Hydrochloride Extended-release Tablets
ANDA 79-087

To Whom It May Concern:

This is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and (ii) (§§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax Laboratories, Inc. ("Impax"), a Delaware corporation with its principal place of business at 30831 Huntwood Avenue, Hayward, California, 94544, has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent No. 7,276,250.

A detailed statement of the factual and legal bases for Impax's position regarding this patent is provided herein. Impax reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patent is invalid, unenforceable, or not infringed.

An Offer of Confidential Access to Impax's ANDA 79-087, pursuant to 21 U.S.C. §355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Permission to use Federal Express for delivery of this notice and detailed statement was granted by Martin Shimer of the Office of Generic Drugs on September 24, 2007.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance

MCS/aks

Enclosures: Impax Laboratories, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patent No. 7,276,250 Is Invalid, Unenforceable Or Not Infringed

Impax Laboratories, Inc.'s Offer of Confidential Access to ANDA 79-087

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NO. 7,276,250 IS NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

This is the detailed statement of Impax Laboratories, Inc. ("Impax"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal basis for Impax's opinion that U.S. Patent No. 7,276,250 is invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, importation, use or sale of Impax's Oxymorphone HCl Extended Release 5 mg, 10 mg, 20 mg, and 40 mg tablets ("Impax Oxymorphone ER"), for which this detailed statement is submitted. Impax's factual and legal bases are set forth below.

I. Applicable Legal Standards

A U.S. patent gives the owner the right to preclude others from making, using or selling the invention defined by the claims of the patent in the United States and its territories for the term of the patent.[1] Those making, using or selling an invention defined by the claims of a patent are said to be directly infringing the claims of the patent. The patent statute also describes remedies for contributory infringement and inducement of infringement.[2] For there to be indirect infringement by one party, there must be direct infringement by another party. Furthermore, the act of filing an ANDA with patent invalidity or non-infringement certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) may create a cause of action for patent infringement.[3]

Evaluating infringement is a two-step process. First, the scope of the claims is determined, and second, the accused product or process is compared to the properly interpreted claims. The claims, properly construed as a matter of law by the court,[4] are the measure of the grant of the exclusive right to the patentee, and set out the metes and bounds of the invention.[5]

Claim construction may involve the use of both intrinsic and extrinsic evidence; however, the Federal Circuit in an *en banc* decision stressed the importance of giving the appropriate weight to such evidence.[6] In particular, the Federal Circuit has instructed trial courts that as a starting point, claim terms are to be given their ordinary and customary meaning as understood by one of ordinary skill in the art.[7] In determining the ordinary and customary meaning, the trial

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[1] 35 U.S.C. § 271(a).

[2] 35 U.S.C. § 271(b) & (c).

[3] 35 U.S.C. § 271(e)(2)(A).

[4] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995)(*en banc*), *aff'd*, 517 U.S. 370 (1996); *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

[5] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004).

[6] *Phillips v. AWH Corp. et al.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*).

[7] *Innova*, 381 F.3d at 1116; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

court must first consider the claim term not only in the context of the particular claim, but also in the context of the rest of the claims, the specification, and the prosecution history.[8]

Once the language of the claims is properly interpreted, the claims must be "read on" the accused structure to determine whether each of the limitations recited in the claim is present.[9] Under the "all-elements" rule, a claim is not infringed unless each element of the claim, or a substantial equivalent of that element, is found in the accused device[10] When any limitation recited in a claim is not met, literal infringement is avoided.[11]

The absence of literal infringement does not necessarily mean that a process or device does not infringe a patent. The judicially created "doctrine of equivalents" allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes.[12] Thus, even though the language of a claim cannot be read literally upon a process or device, a claim can be infringed if the process or device "performs substantially the same function in substantially the same way to obtain the same result."[13] What constitutes "equivalency" must be determined against the context of the patent, the prior art, and the particular circumstances of the case.

A patent and each of its issued claims is presumed to be valid.[14] Proof of invalidity of a patent or its claims is a complete defense to a charge of infringement of the claims of that patent. The claims of a patent can be found to be invalid under 35 U.S.C. §103 because they are obvious in light of the prior art. With respect to patent claim invalidity, "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

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[8] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005); *Vitronics*, 90 F.3d at 1582-83 (Fed. Cir. 1996).

[9] *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989).

[10] *Pennwalt Corp. v. Durand-Wayland Co.*, 833 F.2d 931, 935, (Fed. Cir. 1987); *Corning Glass Works*, 868 F.2d at 1259.

[11] *Lemelson v. United States*, 752 F.2d 1538 (Fed. Cir. 1985). See also, *Cooper Cameron Corp. v. Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317 (Fed. Cir. 2002).

[12] *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. et al.*, 535 U.S. 722, 723 (2002).

[13] *Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). See also *Jonnson v. Stanley Works*, 711 F. Supp. 1395, 1407 (N.D. Ohio, 1989), *aff'd*, 903 F.2d 812 (Fed. Cir. 1990); *Fantasy Sports Properties, Inc. v. SportsLine.com, Inc.*, 287 F.3d 1108 (Fed. Cir. 2002).

[14] 35 U.S.C. § 282.

a person having ordinary skill in the art to which said subject matter pertains."[15] The "combination of familiar elements according to known methods" is likely be obvious when it yields predictable results, and common sense, not a "formalistic conception of the words teaching, suggestion, and motivation" should guide obviousness analysis.[16] Factors to be considered in determining obviousness include the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the art, and secondary considerations.[17]

A patent application must describe how to make and use the invention in such full, clear, concise and exact terms as to enable any person of ordinary skill in the art to which it pertains to make and use the same.[18] For a claim to be enabled, the disclosure must be sufficiently described as to enable one of ordinary skill in the art to practice the invention without undue experimentation. A patent can be enabled even if it requires some experimentation to practice the invention: what is proscribed is undue experimentation.

Furthermore, the specification must be enabled at the time of filing the application, and a later filed publication cannot supplement an insufficient disclosure to render it enabling.[19] Later filed publications can be considered as evidence of the level of ordinary skill in the art at the time of filing the application, reinforcing the standard that the issue is whether one skilled in the art would have believed the application to be enabled at the time of filing. *In re Wands* set out 8 factors to be considered for enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill in the art, (5) the level of predictability in the art, (6) the amount of direction provided in the application, (7) the existence of working examples in the specification, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.[20]

In order for a claim to be patentable, it also must meet the written description requirements of 35 U.S.C. § 112, Paragraph 1. The goals of the written description requirement are to (1) convey to the public what was invented, (2) put the public in possession of what the applicant claims as the invention, and (3) prevent an applicant from claiming subject matter that

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[15] 35 U.S.C. § 103(a).

[16] *KSR Int'l Co. v. Teleflex Inc., et al.*, 127 S.Ct. 1727, 1739-41 (2007).

[17] *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

[18] *See* 35 U.S.C. §112, 1st paragraph.

[19] *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

[20] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

was not described in the specification as filed. As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing."[21] Possession of the invention is shown by describing the invention with specificity such as by words, structures, figures, diagrams, and formulas.[22]

The second paragraph of §112 requires the specification of a patent to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[23] To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim.[24] Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [the Federal Circuit Court has] asked is that the claims be amenable to construction, however difficult that task may be."[25]

Furthermore, a patent may be rendered unenforceable for inequitable conduct. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith, and honesty.'"[26] "To hold a patent unenforceable due to inequitable conduct, there must be clear and convincing evidence that the applicant (1) made an affirmative misrepresentation or material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]."[27] Intent need not, and rarely can, be proven by direct evidence.[28] "[I]n the absence of a credible explanation, intent to deceive *is generally inferred* from the facts and circumstances surrounding a knowing failure to disclose material information."[29] Further, the Federal Circuit recently "made it clear that 'a patentee facing a high level of materiality and clear proof that it knew or should have known of that

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[21] *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1259 (Fed. Cir. 2004).

[22] Revised Interim Written Description Guidelines, available at <http://www.uspto.gov/web/menu/written.pdf>.

[23] *See* 35 U.S.C. § 112, 2nd paragraph.

[24] *Miles Lab. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[25] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[26] *Ferring B.V. v. Barr Labs*, 437 F.3d 1181, 1186-87 (Fed. Cir. 2006) (quoting *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005)).

[27] *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007).

[28] *Merck & Co., Inc. v. Danbury Pharmacal, Inc.* 873 F.2d 1418, 1422 (Fed. Cir. 1989).

[29] *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead.'"[30]

II. U.S. Patent No. 7,276,250

U.S. Patent No. 7,276,250 (the "'250 patent") was filed on July 3, 2002 and issued on October 2, 2007. The '250 patent claims priority to U.S. Provisional Application No. 60/329,352, filed October 15, 2001, U.S. Provisional Application No. 60/329,426, filed October 15, 2001, and U.S. Provisional Application No. 60/303,357, filed July 6, 2001. The '250 patent is assigned to Penwest Pharmaceuticals Company of Patterson, New York.

A. The Claims of the '250 patent

There are sixteen claims issued in the '250 patent, which read as follows:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim 1, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim 1, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

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[30] *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997)).

5. The oral sustained release formulation of claim 1, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 1-5.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim 7, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim 7, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim 7, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim 7, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 7-11.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 1-5.

14. The solid dosage formulation of claim 13, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 7-11.

16. The solid dosage formulation of claim 15, wherein the solid dosage formulation is a tablet.

B. No Infringement of the Claims of the '250 patent

The '250 patent contains only 3 independent claims. Each of the independent claims 1, 4, and 7 of the '250 patent contains the specific limitation that the composition must include dextrose, among other ingredients. Specifically, the compositions of claims 1 and 7 require "about 20% to about 55% by weight dextrose." The composition of claim 4 requires "about 35% dextrose." Because each remaining claim contains the limitations of the independent claim from it depends, all of the claims in the '250 patent require the presence of dextrose, in the respective amounts claimed, for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claims of the '250 patent because Impax Oxymorphone ER does not contain dextrose in the claimed amounts. Furthermore, Impax's Oxymorphone ER would not infringe any claim under the doctrine of equivalents. Patentees are entitled to no range of equivalents around the "about 20% to about 55% by weight dextrose" and "about 35% dextrose" claim limitations. During prosecution, in order to obtain allowance, claims requiring "at least one pharmaceutical diluent" were cancelled in favor of the narrower claims specifying dextrose in the amounts listed above. Applicants are estopped from arguing equivalents to these claim limitations as no exceptions to the complete bar to the doctrine of equivalents apply in this case. Therefore, the Impax Oxymorphone ER does not contain any equivalent to the amounts of dextrose claimed in the '250 patent.

C. Conclusion

For the reasons stated above, none of the claims of U.S. Patent No. 7,276,250 are infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER. Impax reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable or not infringed.

ABBREVIATED NEW DRUG APPLICATION 79-087
OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Impax Laboratories, Inc. ("Impax") has provided notice to Endo Pharmaceuticals Inc. (hereinafter "Recipient") that Impax submitted to the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application No. 79-087 for Impax's Oxymorphone Hydrochloride Extended-release Tablets, (hereinafter referred to in whole or in part as the "ANDA"), containing a Paragraph IV certification with respect to U.S. Patent No. 7,276,250 (the "Listed Patent") which is listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations;" and

WHEREAS this document constitutes Impax's Offer of Confidential Access to that ANDA pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

WHEREAS Impax offers to provide Recipient confidential access to the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

WHEREAS this document accompanies Impax's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patent;

NOW, THEREFORE, Impax makes this offer:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions recited in clause 2 below, Impax hereby provides Recipient this Offer of Confidential Access for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to the Listed Patent.

2. The right of confidential access offered herein is subject to the following restrictions as to persons entitled to access, and the use and disposition of any information accessed, pursuant to this Offer of Confidential Access:

   A. **Persons Entitled to Access**: Persons entitled to access (hereinafter referred to as "Authorized Evaluators") under this Offer of Confidential Access are restricted to

outside counsel engaged by Recipient to represent Recipient and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that:

i. Such outside counsel has been identified to Impax in writing;

ii. Such outside counsel is not involved in patent prosecution matters for Recipient;

iii. Within five (5) business days of receiving such written identification, Impax has not objected, in writing, to provision of confidential access to the identified outside counsel.

B. **Materials Accessible by Authorized Evaluators**: A copy of the ANDA, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. **Use of the ANDA and Information in the ANDA**:

i. Subject to paragraph 2(D)(ii)(a), use of the ANDA, and all information contained therein or derived therefrom, and all notes, analyses, studies, or documents prepared by Authorized Evaluators to the extent they reflect the contents of the ANDA furnished herein, is for the sole and limited purpose of evaluating possible infringement of the Listed Patent and for no other purpose.

ii. Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information in the ANDA, to any person other than an Authorized Evaluator.

iii. Notwithstanding the provisions of subparagraphs 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Recipient on whether or not to assert the Listed Patent, provided, however, that the information in the ANDA is not thereby disclosed.

D. **Disposition of the Information in the ANDA:**

i. If Recipient does not assert the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Authorized Evaluators shall, and Recipient shall direct and ensure that Authorized Evaluators, within thirty (30) days after the expiration of the 45-day period, destroy or send to Impax the portions of the ANDA provided, and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, and Recipient or Authorized Evaluators shall notify Impax that this has been done.

ii. Recipient agrees that if Recipient asserts the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement which this offer accompanies:

a. While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Impax. Until such a protective order is entered, subsection 2(C)(ii) above continues to apply.

b. Recipient shall direct and ensure that Authorized Evaluators destroy the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, within thirty (30) days after the final determination of the action brought against Impax.

iii. Notwithstanding the provisions of subparagraphs 2(D)(i) and 2(D)(ii) above, the Authorized Evaluators identified in subparagraph 2(A) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document prepared by Authorized Evaluators to the extent that they reflect information in the ANDA.

E. **Accidental Disclosure:** Should information from the ANDA be disclosed, inadvertently or otherwise, Recipient shall, at Recipient's earliest opportunity, contact Impax and identify:

i. What has been disclosed;

ii. The individuals to whom such information has been disclosed; and

iii. Steps taken by Recipient and Authorized Evaluators to ensure the information in the ANDA continues to be treated pursuant to the terms of this agreement and is not further disseminated.

3. Recipient and Authorized Evaluators recognize that violation of any provision of this Offer of Confidential Access will cause irreparable injury to Impax, and that an adequate legal remedy does not exist. Impax, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipient and Authorized Evaluators from violating the terms of this Offer of Confidential Access. It is further agreed that in such an action Impax is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer of Confidential Access be found by a court of competent jurisdiction to be illegal, unconstitutional and/or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the information in the ANDA, except for the purpose expressly stated herein.

6. This Agreement shall be governed by the laws of the State of California, without giving effect to its conflicts of law or choice of law principles.

7. Each of Recipient, Authorized Evaluators and Impax, irrevocably submit to and accept, generally and unconditionally, the exclusive personal jurisdiction of the courts of the State of California, and of the U.S. District Court for the Northern District of California, waives its right to assert any objection or defense based on venue or *forum non conveniens* and agrees to be bound by any judgment rendered thereby arising under or in respect of this Agreement.

8. When accepted by the parties hereto, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

9. An Authorized Evaluator may request access to the ANDA by executing one copy of this Confidential Access Agreement where indicated and returning the executed copy to Impax within the 45-day period. Thereupon, the terms contained in this document shall be considered an enforceable contract between Impax and the Recipient.

Impax Laboratories, Inc.

Charles Hildenbrand, Sr. Vice-President of Operations

Date: 27 Sept, 2007

Recipient
By its authorized agent(s):

Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____, 2007

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue Hayward, CA 94544
Phone (510) 476-2000 Fax (510) 476-2092

October 5, 2007

Via Federal Express

Endo Pharmaceuticals Inc.
100 Endo Blvd.
Chadds Ford, PA 19317

Tracking # 8613 5929 4963

Penwest Pharmaceuticals Co.
39 Old Ridgebury Rd., Suite 11
Danbury, CT 06810

Tracking # 8613 5929 4974

Re: Patent Certification Notice – U.S. Patent No. 7,276,250
Oxymorphone Hydrochloride Extended-release Tablets
ANDA 79-087

To Whom It May Concern:

This is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and (ii) (§§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax Laboratories, Inc. ("Impax"), a Delaware corporation with its principal place of business at 30831 Huntwood Avenue, Hayward, California, 94544, has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent No. 7,276,250.

A detailed statement of the factual and legal bases for Impax's position regarding this patent is provided herein. Impax reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patent is invalid, unenforceable, or not infringed.

An Offer of Confidential Access to Impax's ANDA 79-087, pursuant to 21 U.S.C. §355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Permission to use Federal Express for delivery of this notice and detailed statement was granted by Martin Shimer of the Office of Generic Drugs on September 24, 2007.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance

MCS/aks

Enclosures: Impax Laboratories, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patent No. 7,276,250 Is Invalid, Unenforceable Or Not Infringed

Impax Laboratories, Inc.'s Offer of Confidential Access to ANDA 79-087

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NO. 7,276,250 IS NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

This is the detailed statement of Impax Laboratories, Inc. ("Impax"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal basis for Impax's opinion that U.S. Patent No. 7,276,250 is invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, importation, use or sale of Impax's Oxymorphone HCl Extended Release 5 mg, 10 mg, 20 mg, and 40 mg tablets ("Impax Oxymorphone ER"), for which this detailed statement is submitted. Impax's factual and legal bases are set forth below.

I. Applicable Legal Standards

A U.S. patent gives the owner the right to preclude others from making, using or selling the invention defined by the claims of the patent in the United States and its territories for the term of the patent.[1] Those making, using or selling an invention defined by the claims of a patent are said to be directly infringing the claims of the patent. The patent statute also describes remedies for contributory infringement and inducement of infringement.[2] For there to be indirect infringement by one party, there must be direct infringement by another party. Furthermore, the act of filing an ANDA with patent invalidity or non-infringement certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) may create a cause of action for patent infringement.[3]

Evaluating infringement is a two-step process. First, the scope of the claims is determined, and second, the accused product or process is compared to the properly interpreted claims. The claims, properly construed as a matter of law by the court,[4] are the measure of the grant of the exclusive right to the patentee, and set out the metes and bounds of the invention.[5]

Claim construction may involve the use of both intrinsic and extrinsic evidence; however, the Federal Circuit in an *en banc* decision stressed the importance of giving the appropriate weight to such evidence.[6] In particular, the Federal Circuit has instructed trial courts that as a starting point, claim terms are to be given their ordinary and customary meaning as understood by one of ordinary skill in the art.[7] In determining the ordinary and customary meaning, the trial

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[1] 35 U.S.C. § 271(a).

[2] 35 U.S.C. § 271(b) & (c).

3 35 U.S.C. § 271(e)(2)(A).

[4] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995)(*en banc*), *aff'd*, 517 U.S. 370 (1996); *Networld, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

[5] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004).

[6] *Phillips v. AWH Corp. et al.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*).

[7] *Innova*, 381 F.3d at 1116; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

court must first consider the claim term not only in the context of the particular claim, but also in the context of the rest of the claims, the specification, and the prosecution history.[8]

Once the language of the claims is properly interpreted, the claims must be "read on" the accused structure to determine whether each of the limitations recited in the claim is present.[9] Under the "all-elements" rule, a claim is not infringed unless each element of the claim, or a substantial equivalent of that element, is found in the accused device[10] When any limitation recited in a claim is not met, literal infringement is avoided.[11]

The absence of literal infringement does not necessarily mean that a process or device does not infringe a patent. The judicially created "doctrine of equivalents" allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes.[12] Thus, even though the language of a claim cannot be read literally upon a process or device, a claim can be infringed if the process or device "performs substantially the same function in substantially the same way to obtain the same result."[13] What constitutes "equivalency" must be determined against the context of the patent, the prior art, and the particular circumstances of the case.

A patent and each of its issued claims is presumed to be valid.[14] Proof of invalidity of a patent or its claims is a complete defense to a charge of infringement of the claims of that patent. The claims of a patent can be found to be invalid under 35 U.S.C. §103 because they are obvious in light of the prior art. With respect to patent claim invalidity, "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

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[8] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005); *Vitronics*, 90 F.3d at 1582-83 (Fed. Cir. 1996).

[9] *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989).

[10] *Pennwalt Corp. v. Durand-Wayland Co.*, 833 F.2d 931, 935, (Fed. Cir. 1987); *Corning Glass Works*, 868 F.2d at 1259.

[11] *Lemelson v. United States*, 752 F.2d 1538 (Fed. Cir. 1985). See also, *Cooper Cameron Corp. v. Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317 (Fed. Cir. 2002).

[12] *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. et al.*, 535 U.S. 722, 723 (2002).

[13] *Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). See also *Jonnson v. Stanley Works*, 711 F. Supp. 1395, 1407 (N.D. Ohio, 1989), *aff'd*, 903 F.2d 812 (Fed. Cir. 1990); *Fantasy Sports Properties, Inc. v. SportsLine.com, Inc.*, 287 F.3d 1108 (Fed. Cir. 2002).

[14] 35 U.S.C. § 282.

a person having ordinary skill in the art to which said subject matter pertains."[15] The "combination of familiar elements according to known methods" is likely be obvious when it yields predictable results, and common sense, not a "formalistic conception of the words teaching, suggestion, and motivation" should guide obviousness analysis.[16] Factors to be considered in determining obviousness include the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the art, and secondary considerations.[17]

A patent application must describe how to make and use the invention in such full, clear, concise and exact terms as to enable any person of ordinary skill in the art to which it pertains to make and use the same.[18] For a claim to be enabled, the disclosure must be sufficiently described as to enable one of ordinary skill in the art to practice the invention without undue experimentation. A patent can be enabled even if it requires some experimentation to practice the invention: what is proscribed is undue experimentation.

Furthermore, the specification must be enabled at the time of filing the application, and a later filed publication cannot supplement an insufficient disclosure to render it enabling.[19] Later filed publications can be considered as evidence of the level of ordinary skill in the art at the time of filing the application, reinforcing the standard that the issue is whether one skilled in the art would have believed the application to be enabled at the time of filing. *In re Wands* set out 8 factors to be considered for enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill in the art, (5) the level of predictability in the art, (6) the amount of direction provided in the application, (7) the existence of working examples in the specification, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.[20]

In order for a claim to be patentable, it also must meet the written description requirements of 35 U.S.C. § 112, Paragraph 1. The goals of the written description requirement are to (1) convey to the public what was invented, (2) put the public in possession of what the applicant claims as the invention, and (3) prevent an applicant from claiming subject matter that

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[15] 35 U.S.C. § 103(a).

[16] *KSR Int'l Co. v. Teleflex Inc., et al.*, 127 S.Ct. 1727, 1739-41 (2007).

[17] *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

[18] *See* 35 U.S.C. §112, 1st paragraph.

[19] *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

[20] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

was not described in the specification as filed. As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing."[21] Possession of the invention is shown by describing the invention with specificity such as by words, structures, figures, diagrams, and formulas.[22]

The second paragraph of §112 requires the specification of a patent to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[23] To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim.[24] Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [the Federal Circuit Court has] asked is that the claims be amenable to construction, however difficult that task may be."[25]

Furthermore, a patent may be rendered unenforceable for inequitable conduct. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith, and honesty.'"[26] "To hold a patent unenforceable due to inequitable conduct, there must be clear and convincing evidence that the applicant (1) made an affirmative misrepresentation or material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]."[27] Intent need not, and rarely can, be proven by direct evidence.[28] "[I]n the absence of a credible explanation, intent to deceive *is generally inferred* from the facts and circumstances surrounding a knowing failure to disclose material information."[29] Further, the Federal Circuit recently "made it clear that 'a patentee facing a high level of materiality and clear proof that it knew or should have known of that

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[21] *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1259 (Fed. Cir. 2004).

[22] Revised Interim Written Description Guidelines, available at <http://www.uspto.gov/web/menu/written.pdf>.

[23] *See* 35 U.S.C. § 112, 2nd paragraph.

[24] *Miles Lab. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[25] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[26] *Ferring B.V. v. Barr Labs,* 437 F.3d 1181, 1186-87 (Fed. Cir. 2006) (quoting *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005)).

[27] *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007).

[28] *Merck & Co., Inc. v. Danbury Pharmacal, Inc.* 873 F.2d 1418, 1422 (Fed. Cir. 1989).

[29] *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead.'"[30]

II. U.S. Patent No. 7,276,250

U.S. Patent No. 7,276,250 (the "'250 patent") was filed on July 3, 2002 and issued on October 2, 2007. The '250 patent claims priority to U.S. Provisional Application No. 60/329,352, filed October 15, 2001, U.S. Provisional Application No. 60/329,426, filed October 15, 2001, and U.S. Provisional Application No. 60/303,357, filed July 6, 2001. The '250 patent is assigned to Penwest Pharmaceuticals Company of Patterson, New York.

A. The Claims of the '250 patent

There are sixteen claims issued in the '250 patent, which read as follows:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim 1, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim 1, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

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[30] *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997)).

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NO. 7,276,250 IS NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

5. The oral sustained release formulation of claim 1, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 1-5.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim 7, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim 7, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim 7, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim 7, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 7-11.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 1-5.

14. The solid dosage formulation of claim 13, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 7-11.

16. The solid dosage formulation of claim 15, wherein the solid dosage formulation is a tablet.

B. No Infringement of the Claims of the '250 patent

The '250 patent contains only 3 independent claims. Each of the independent claims 1, 4, and 7 of the '250 patent contains the specific limitation that the composition must include dextrose, among other ingredients. Specifically, the compositions of claims 1 and 7 require "about 20% to about 55% by weight dextrose." The composition of claim 4 requires "about 35% dextrose." Because each remaining claim contains the limitations of the independent claim from it depends, all of the claims in the '250 patent require the presence of dextrose, in the respective amounts claimed, for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claims of the '250 patent because Impax Oxymorphone ER does not contain dextrose in the claimed amounts. Furthermore, Impax's Oxymorphone ER would not infringe any claim under the doctrine of equivalents. Patentees are entitled to no range of equivalents around the "about 20% to about 55% by weight dextrose" and "about 35% dextrose" claim limitations. During prosecution, in order to obtain allowance, claims requiring "at least one pharmaceutical diluent" were cancelled in favor of the narrower claims specifying dextrose in the amounts listed above. Applicants are estopped from arguing equivalents to these claim limitations as no exceptions to the complete bar to the doctrine of equivalents apply in this case. Therefore, the Impax Oxymorphone ER does not contain any equivalent to the amounts of dextrose claimed in the '250 patent.

C. Conclusion

For the reasons stated above, none of the claims of U.S. Patent No. 7,276,250 are infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER. Impax reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable or not infringed.

ABBREVIATED NEW DRUG APPLICATION 79-087
OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Impax Laboratories, Inc. ("Impax") has provided notice to Endo Pharmaceuticals Inc. (hereinafter "Recipient") that Impax submitted to the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application No. 79-087 for Impax's Oxymorphone Hydrochloride Extended-release Tablets, (hereinafter referred to in whole or in part as the "ANDA"), containing a Paragraph IV certification with respect to U.S. Patent No. 7,276,250 (the "Listed Patent") which is listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations;" and

WHEREAS this document constitutes Impax's Offer of Confidential Access to that ANDA pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

WHEREAS Impax offers to provide Recipient confidential access to the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

WHEREAS this document accompanies Impax's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patent;

NOW, THEREFORE, Impax makes this offer:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions recited in clause 2 below, Impax hereby provides Recipient this Offer of Confidential Access for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to the Listed Patent.

2. The right of confidential access offered herein is subject to the following restrictions as to persons entitled to access, and the use and disposition of any information accessed, pursuant to this Offer of Confidential Access:

   A. **Persons Entitled to Access**: Persons entitled to access (hereinafter referred to as "Authorized Evaluators") under this Offer of Confidential Access are restricted to

outside counsel engaged by Recipient to represent Recipient and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that:

i. Such outside counsel has been identified to Impax in writing;

ii. Such outside counsel is not involved in patent prosecution matters for Recipient;

iii. Within five (5) business days of receiving such written identification, Impax has not objected, in writing, to provision of confidential access to the identified outside counsel.

B. Materials Accessible by Authorized Evaluators: A copy of the ANDA, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. Use of the ANDA and Information in the ANDA:

i. Subject to paragraph 2(D)(ii)(a), use of the ANDA, and all information contained therein or derived therefrom, and all notes, analyses, studies, or documents prepared by Authorized Evaluators to the extent they reflect the contents of the ANDA furnished herein, is for the sole and limited purpose of evaluating possible infringement of the Listed Patent and for no other purpose.

ii. Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information in the ANDA, to any person other than an Authorized Evaluator.

iii. Notwithstanding the provisions of subparagraphs 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Recipient on whether or not to assert the Listed Patent, provided, however, that the information in the ANDA is not thereby disclosed.

D. Disposition of the Information in the ANDA:

i. If Recipient does not assert the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Authorized Evaluators shall, and Recipient shall direct and ensure that Authorized Evaluators, within thirty (30) days after the expiration of the 45-day period, destroy or send to Impax the portions of the ANDA provided, and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, and Recipient or Authorized Evaluators shall notify Impax that this has been done.

ii. Recipient agrees that if Recipient asserts the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement which this offer accompanies:

a. While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Impax. Until such a protective order is entered, subsection 2(C)(ii) above continues to apply.

b. Recipient shall direct and ensure that Authorized Evaluators destroy the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, within thirty (30) days after the final determination of the action brought against Impax.

iii. Notwithstanding the provisions of subparagraphs 2(D)(i) and 2(D)(ii) above, the Authorized Evaluators identified in subparagraph 2(A) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document prepared by Authorized Evaluators to the extent that they reflect information in the ANDA.

E. **Accidental Disclosure:** Should information from the ANDA be disclosed, inadvertently or otherwise, Recipient shall, at Recipient's earliest opportunity, contact Impax and identify:

i. What has been disclosed;

ii. The individuals to whom such information has been disclosed; and

iii. Steps taken by Recipient and Authorized Evaluators to ensure the information in the ANDA continues to be treated pursuant to the terms of this agreement and is not further disseminated.

3. Recipient and Authorized Evaluators recognize that violation of any provision of this Offer of Confidential Access will cause irreparable injury to Impax, and that an adequate legal remedy does not exist. Impax, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipient and Authorized Evaluators from violating the terms of this Offer of Confidential Access. It is further agreed that in such an action Impax is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer of Confidential Access be found by a court of competent jurisdiction to be illegal, unconstitutional and/or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the information in the ANDA, except for the purpose expressly stated herein.

6. This Agreement shall be governed by the laws of the State of California, without giving effect to its conflicts of law or choice of law principles.

7. Each of Recipient, Authorized Evaluators and Impax, irrevocably submit to and accept, generally and unconditionally, the exclusive personal jurisdiction of the courts of the State of California, and of the U.S. District Court for the Northern District of California, waives its right to assert any objection or defense based on venue or *forum non conveniens* and agrees to be bound by any judgment rendered thereby arising under or in respect of this Agreement.

8. When accepted by the parties hereto, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

9. An Authorized Evaluator may request access to the ANDA by executing one copy of this Confidential Access Agreement where indicated and returning the executed copy to Impax within the 45-day period. Thereupon, the terms contained in this document shall be considered an enforceable contract between Impax and the Recipient.

Impax Laboratories, Inc.

Charles Hildenbrand, Sr. Vice-President of Operations

Date: 27 Sept, 2007

Recipient
By its authorized agent(s):

Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____, 2007

30831 Huntwood Avenue Hayward, CA 94544
Phone (510) 476-2000 Fax (510) 476-2092

October 9, 2007

Via Federal Express

Endo Pharmaceuticals Inc.
100 Endo Blvd.
Chadds Ford, PA 19317

Tracking # 8613 5929 5000

Penwest Pharmaceuticals Co.
39 Old Ridgebury Rd., Suite 11
Danbury, CT 06810

Tracking # 8613 5929 5010

Re: Patent Certification Notice – U.S. Patent No. 7,276,250
Oxymorphone Hydrochloride Extended-release Tablets
ANDA 79-087

To Whom It May Concern:

This is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and (ii) (§§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax Laboratories, Inc. ("Impax"), a Delaware corporation with its principal place of business at 30831 Huntwood Avenue, Hayward, California, 94544, has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent No. 7,276,250.

A detailed statement of the factual and legal bases for Impax's position regarding this patent is provided herein. Impax reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patent is invalid, unenforceable, or not infringed.

An Offer of Confidential Access to Impax's ANDA 79-087, pursuant to 21 U.S.C. §355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Permission to use Federal Express for delivery of this notice and detailed statement was granted by Martin Shimer of the Office of Generic Drugs on September 24, 2007.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance

MCS/aks

Enclosures: Impax Laboratories, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patent No. 7,276,250 Is Invalid, Unenforceable Or Not Infringed

Impax Laboratories, Inc.'s Offer of Confidential Access to ANDA 79-087

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NO. 7,276,250 IS NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

This is the detailed statement of Impax Laboratories, Inc. ("Impax"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal basis for Impax's opinion that U.S. Patent No. 7,276,250 is invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, importation, use or sale of Impax's Oxymorphone HCl Extended Release 5 mg, 10 mg, 20 mg, and 40 mg tablets ("Impax Oxymorphone ER"), for which this detailed statement is submitted. Impax's factual and legal bases are set forth below.

I. Applicable Legal Standards

A U.S. patent gives the owner the right to preclude others from making, using or selling the invention defined by the claims of the patent in the United States and its territories for the term of the patent.[1] Those making, using or selling an invention defined by the claims of a patent are said to be directly infringing the claims of the patent. The patent statute also describes remedies for contributory infringement and inducement of infringement.[2] For there to be indirect infringement by one party, there must be direct infringement by another party. Furthermore, the act of filing an ANDA with patent invalidity or non-infringement certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) may create a cause of action for patent infringement.[3]

Evaluating infringement is a two-step process. First, the scope of the claims is determined, and second, the accused product or process is compared to the properly interpreted claims. The claims, properly construed as a matter of law by the court,[4] are the measure of the grant of the exclusive right to the patentee, and set out the metes and bounds of the invention.[5]

Claim construction may involve the use of both intrinsic and extrinsic evidence; however, the Federal Circuit in an *en banc* decision stressed the importance of giving the appropriate weight to such evidence.[6] In particular, the Federal Circuit has instructed trial courts that as a starting point, claim terms are to be given their ordinary and customary meaning as understood by one of ordinary skill in the art.[7] In determining the ordinary and customary meaning, the trial

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[1] 35 U.S.C. § 271(a).

[2] 35 U.S.C. § 271(b) & (c).

3 35 U.S.C. § 271(e)(2)(A).

[4] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995)(*en banc*), *aff'd*, 517 U.S. 370 (1996); *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

[5] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004).

[6] *Phillips v. AWH Corp. et al.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*).

[7] *Innova*, 381 F.3d at 1116; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

court must first consider the claim term not only in the context of the particular claim, but also in the context of the rest of the claims, the specification, and the prosecution history.[8]

Once the language of the claims is properly interpreted, the claims must be "read on" the accused structure to determine whether each of the limitations recited in the claim is present.[9] Under the "all-elements" rule, a claim is not infringed unless each element of the claim, or a substantial equivalent of that element, is found in the accused device[10] When any limitation recited in a claim is not met, literal infringement is avoided.[11]

The absence of literal infringement does not necessarily mean that a process or device does not infringe a patent. The judicially created "doctrine of equivalents" allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes.[12] Thus, even though the language of a claim cannot be read literally upon a process or device, a claim can be infringed if the process or device "performs substantially the same function in substantially the same way to obtain the same result."[13] What constitutes "equivalency" must be determined against the context of the patent, the prior art, and the particular circumstances of the case.

A patent and each of its issued claims is presumed to be valid.[14] Proof of invalidity of a patent or its claims is a complete defense to a charge of infringement of the claims of that patent. The claims of a patent can be found to be invalid under 35 U.S.C. §103 because they are obvious in light of the prior art. With respect to patent claim invalidity, "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

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[8] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005); *Vitronics*, 90 F.3d at 1582-83 (Fed. Cir. 1996).

[9] *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989).

[10] *Pennwalt Corp. v. Durand-Wayland Co.*, 833 F.2d 931, 935, (Fed. Cir. 1987); *Corning Glass Works*, 868 F.2d at 1259.

[11] *Lemelson v. United States*, 752 F.2d 1538 (Fed. Cir. 1985). See also, *Cooper Cameron Corp. v. Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317 (Fed. Cir. 2002).

[12] *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. et al.*, 535 U.S. 722, 723 (2002).

[13] *Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). See also *Jonnson v. Stanley Works*, 711 F. Supp. 1395, 1407 (N.D. Ohio, 1989), *aff'd*, 903 F.2d 812 (Fed. Cir. 1990); *Fantasy Sports Properties, Inc. v. SportsLine.com, Inc.*, 287 F.3d 1108 (Fed. Cir. 2002).

[14] 35 U.S.C. § 282.

a person having ordinary skill in the art to which said subject matter pertains."[15] The "combination of familiar elements according to known methods" is likely be obvious when it yields predictable results, and common sense, not a "formalistic conception of the words teaching, suggestion, and motivation" should guide obviousness analysis.[16] Factors to be considered in determining obviousness include the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the art, and secondary considerations.[17]

A patent application must describe how to make and use the invention in such full, clear, concise and exact terms as to enable any person of ordinary skill in the art to which it pertains to make and use the same.[18] For a claim to be enabled, the disclosure must be sufficiently described as to enable one of ordinary skill in the art to practice the invention without undue experimentation. A patent can be enabled even if it requires some experimentation to practice the invention: what is proscribed is undue experimentation.

Furthermore, the specification must be enabled at the time of filing the application, and a later filed publication cannot supplement an insufficient disclosure to render it enabling.[19] Later filed publications can be considered as evidence of the level of ordinary skill in the art at the time of filing the application, reinforcing the standard that the issue is whether one skilled in the art would have believed the application to be enabled at the time of filing. *In re Wands* set out 8 factors to be considered for enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill in the art, (5) the level of predictability in the art, (6) the amount of direction provided in the application, (7) the existence of working examples in the specification, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.[20]

In order for a claim to be patentable, it also must meet the written description requirements of 35 U.S.C. § 112, Paragraph 1. The goals of the written description requirement are to (1) convey to the public what was invented, (2) put the public in possession of what the applicant claims as the invention, and (3) prevent an applicant from claiming subject matter that

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[15] 35 U.S.C. § 103(a).

[16] *KSR Int'l Co. v. Teleflex Inc., et al.*, 127 S.Ct. 1727, 1739-41 (2007).

[17] *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

[18] *See* 35 U.S.C. §112, 1st paragraph.

[19] *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

[20] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

was not described in the specification as filed. As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing."[21] Possession of the invention is shown by describing the invention with specificity such as by words, structures, figures, diagrams, and formulas.[22]

The second paragraph of §112 requires the specification of a patent to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[23] To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim.[24] Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [the Federal Circuit Court has] asked is that the claims be amenable to construction, however difficult that task may be."[25]

Furthermore, a patent may be rendered unenforceable for inequitable conduct. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith, and honesty.'"[26] "To hold a patent unenforceable due to inequitable conduct, there must be clear and convincing evidence that the applicant (1) made an affirmative misrepresentation or material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]."[27] Intent need not, and rarely can, be proven by direct evidence.[28] "[I]n the absence of a credible explanation, intent to deceive *is generally inferred* from the facts and circumstances surrounding a knowing failure to disclose material information."[29] Further, the Federal Circuit recently "made it clear that 'a patentee facing a high level of materiality and clear proof that it knew or should have known of that

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[21] *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1259 (Fed. Cir. 2004).

[22] Revised Interim Written Description Guidelines, available at <http://www.uspto.gov/web/menu/written.pdf>.

[23] *See* 35 U.S.C. § 112, 2nd paragraph.

[24] *Miles Lab. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[25] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[26] *Ferring B.V. v. Barr Labs*, 437 F.3d 1181, 1186-87 (Fed. Cir. 2006) (quoting *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005)).

[27] *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007).

[28] *Merck & Co., Inc. v. Danbury Pharmacal, Inc.* 873 F.2d 1418, 1422 (Fed. Cir. 1989).

[29] *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead.'"[30]

II. U.S. Patent No. 7,276,250

U.S. Patent No. 7,276,250 (the "'250 patent") was filed on July 3, 2002 and issued on October 2, 2007. The '250 patent claims priority to U.S. Provisional Application No. 60/329,352, filed October 15, 2001, U.S. Provisional Application No. 60/329,426, filed October 15, 2001, and U.S. Provisional Application No. 60/303,357, filed July 6, 2001. The '250 patent is assigned to Penwest Pharmaceuticals Company of Patterson, New York.

A. The Claims of the '250 patent

There are sixteen claims issued in the '250 patent, which read as follows:

1. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

2. The oral sustained release formulation of claim 1, comprising about 20 mg oxymorphone hydrochloride.

3. The oral sustained release formulation of claim 1, comprising about 160 mg of the granulated sustained release delivery system.

4. An oral sustained release formulation comprising from about 5 to about 80 mg oxymorphone hydrochloride and from about 80 mg to about 360 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

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[30] *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997)).

5. The oral sustained release formulation of claim 1, further comprising an outer coating.

6. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 1-5.

7. An oral sustained release formulation comprising from about 5 mg to about 80 mg oxymorphone hydrochloride and from about 300 mg to about 420 mg of a granulated sustained release delivery system, wherein the granulated sustained release delivery system comprises from about 8.3% to about 41.7% by weight locust bean gum, from about 8.3% to about 41.7% by weight xanthan gum, from about 20% to about 55% by weight dextrose, from about 5% to about 20% by weight calcium sulfate dihydrate, and from about 2% to about 10% ethyl cellulose.

8. The oral sustained release formulation of claim 7, comprising about 20 mg oxymorphone hydrochloride.

9. The oral sustained release formulation of claim 7, comprising about 360 mg of the granulated sustained release delivery system.

10. The oral sustained release formulation of claim 7, wherein the granulated sustained release delivery system comprises about 25% locust bean gum, about 25% xanthan gum, about 35% dextrose, about 10% calcium sulfate dihydrate, and about 5% ethyl cellulose.

11. The oral sustained release formulation of claim 7, further comprising an outer coating.

12. A method for treating a patient suffering from pain comprising administering an effective amount of the oral sustained release formulation of any one of claims 7-11.

13. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 1-5.

14. The solid dosage formulation of claim 13, wherein the solid dosage formulation is a tablet.

15. A solid dosage formulation comprising the oral sustained release formulation of any one of claims 7-11.

16. The solid dosage formulation of claim 15, wherein the solid dosage formulation is a tablet.

B. No Infringement of the Claims of the '250 patent

The '250 patent contains only 3 independent claims. Each of the independent claims 1, 4, and 7 of the '250 patent contains the specific limitation that the composition must include dextrose, among other ingredients. Specifically, the compositions of claims 1 and 7 require "about 20% to about 55% by weight dextrose." The composition of claim 4 requires "about 35% dextrose." Because each remaining claim contains the limitations of the independent claim from it depends, all of the claims in the '250 patent require the presence of dextrose, in the respective amounts claimed, for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claims of the '250 patent because Impax Oxymorphone ER does not contain dextrose in the claimed amounts. Furthermore, Impax's Oxymorphone ER would not infringe any claim under the doctrine of equivalents. Patentees are entitled to no range of equivalents around the "about 20% to about 55% by weight dextrose" and "about 35% dextrose" claim limitations. During prosecution, in order to obtain allowance, claims requiring "at least one pharmaceutical diluent" were cancelled in favor of the narrower claims specifying dextrose in the amounts listed above. Applicants are estopped from arguing equivalents to these claim limitations as no exceptions to the complete bar to the doctrine of equivalents apply in this case. Therefore, the Impax Oxymorphone ER does not contain any equivalent to the amounts of dextrose claimed in the '250 patent.

C. Conclusion

For the reasons stated above, none of the claims of U.S. Patent No. 7,276,250 are infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER. Impax reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable or not infringed.

ABBREVIATED NEW DRUG APPLICATION 79-087
OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Impax Laboratories, Inc. ("Impax") has provided notice to Endo Pharmaceuticals Inc. (hereinafter "Recipient") that Impax submitted to the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application No. 79-087 for Impax's Oxymorphone Hydrochloride Extended-release Tablets, (hereinafter referred to in whole or in part as the "ANDA"), containing a Paragraph IV certification with respect to U.S. Patent No. 7,276,250 (the "Listed Patent") which is listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations;" and

WHEREAS this document constitutes Impax's Offer of Confidential Access to that ANDA pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

WHEREAS Impax offers to provide Recipient confidential access to the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

WHEREAS this document accompanies Impax's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patent;

NOW, THEREFORE, Impax makes this offer:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions recited in clause 2 below, Impax hereby provides Recipient this Offer of Confidential Access for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to the Listed Patent.

2. The right of confidential access offered herein is subject to the following restrictions as to persons entitled to access, and the use and disposition of any information accessed, pursuant to this Offer of Confidential Access:

   A. **Persons Entitled to Access**: Persons entitled to access (hereinafter referred to as "Authorized Evaluators") under this Offer of Confidential Access are restricted to

outside counsel engaged by Recipient to represent Recipient and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that:

i. Such outside counsel has been identified to Impax in writing;

ii. Such outside counsel is not involved in patent prosecution matters for Recipient;

iii. Within five (5) business days of receiving such written identification, Impax has not objected, in writing, to provision of confidential access to the identified outside counsel.

B. Materials Accessible by Authorized Evaluators: A copy of the ANDA, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. Use of the ANDA and Information in the ANDA:

i. Subject to paragraph 2(D)(ii)(a), use of the ANDA, and all information contained therein or derived therefrom, and all notes, analyses, studies, or documents prepared by Authorized Evaluators to the extent they reflect the contents of the ANDA furnished herein, is for the sole and limited purpose of evaluating possible infringement of the Listed Patent and for no other purpose.

ii. Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information in the ANDA, to any person other than an Authorized Evaluator.

iii. Notwithstanding the provisions of subparagraphs 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Recipient on whether or not to assert the Listed Patent, provided, however, that the information in the ANDA is not thereby disclosed.

D. Disposition of the Information in the ANDA:

i. If Recipient does not assert the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Authorized Evaluators shall, and Recipient shall direct and ensure that Authorized Evaluators, within thirty (30) days after the expiration of the 45-day period, destroy or send to Impax the portions of the ANDA provided, and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, and Recipient or Authorized Evaluators shall notify Impax that this has been done.

ii. Recipient agrees that if Recipient asserts the Listed Patent against Impax within forty-five (45) days of receipt of the Notice and Detailed Statement which this offer accompanies:

a. While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Impax. Until such a protective order is entered, subsection 2(C)(ii) above continues to apply.

b. Recipient shall direct and ensure that Authorized Evaluators destroy the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information in the ANDA, within thirty (30) days after the final determination of the action brought against Impax.

iii. Notwithstanding the provisions of subparagraphs 2(D)(i) and 2(D)(ii) above, the Authorized Evaluators identified in subparagraph 2(A) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document prepared by Authorized Evaluators to the extent that they reflect information in the ANDA.

E. **Accidental Disclosure:** Should information from the ANDA be disclosed, inadvertently or otherwise, Recipient shall, at Recipient's earliest opportunity, contact Impax and identify:

i. What has been disclosed;

ii. The individuals to whom such information has been disclosed; and

iii. Steps taken by Recipient and Authorized Evaluators to ensure the information in the ANDA continues to be treated pursuant to the terms of this agreement and is not further disseminated.

3. Recipient and Authorized Evaluators recognize that violation of any provision of this Offer of Confidential Access will cause irreparable injury to Impax, and that an adequate legal remedy does not exist. Impax, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipient and Authorized Evaluators from violating the terms of this Offer of Confidential Access. It is further agreed that in such an action Impax is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer of Confidential Access be found by a court of competent jurisdiction to be illegal, unconstitutional and/or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the information in the ANDA, except for the purpose expressly stated herein.

6. This Agreement shall be governed by the laws of the State of California, without giving effect to its conflicts of law or choice of law principles.

7. Each of Recipient, Authorized Evaluators and Impax, irrevocably submit to and accept, generally and unconditionally, the exclusive personal jurisdiction of the courts of the State of California, and of the U.S. District Court for the Northern District of California, waives its right to assert any objection or defense based on venue or *forum non conveniens* and agrees to be bound by any judgment rendered thereby arising under or in respect of this Agreement.

8. When accepted by the parties hereto, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

9. An Authorized Evaluator may request access to the ANDA by executing one copy of this Confidential Access Agreement where indicated and returning the executed copy to Impax within the 45-day period. Thereupon, the terms contained in this document shall be considered an enforceable contract between Impax and the Recipient.

Impax Laboratories, Inc.

Charles Hildenbrand, Sr. Vice-President of Operations

Date: 27 Sept, 2007

Recipient
By its authorized agent(s):

Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____, 2007

EXHIBIT 7

VIA FEDERAL EXPRESS

October 17, 2007

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance
Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544

Re: Paragraph IV Certification Notice – U.S. Patent No. 7,276,250

Dear Mr. Shaw:

We are writing with reference to your October 2, 2007 letter providing notice that Impax has submitted ANDA 79-087, which includes a Paragraph IV notification with respect to the above-referenced patent.

As an initial matter, we understand from a press release issued by Impax on October 4 that the Food and Drug Administration (FDA) has rescinded its acceptance of the above-referenced ANDA. In light of these public statements by Impax, it appears that Impax's ANDA was not "substantially complete" at the time it was submitted to FDA. Moreover, the predicate required for serving a Paragraph IV Notification, FDA's acceptance of Impax's ANDA, does not exist. *See* 21 CFR 314.95(b). Absent an ANDA that has been accepted by FDA for substantive review, Impax has no legitimate basis to initiate the Paragraph IV process. As a consequence, we believe that the Paragraph IV Notification you have sent to Endo and Penwest is null, void, and without legal effect, including with respect to the 45-day time period referenced in 21 U.S.C. §§ 355(j)(5)(B)(iii) and 355(j)(5)(C).

Nevertheless, Impax has continued to send additional Paragraph IV Notifications even after issuing its press release, in direct violation of FDA regulations. Impax's conduct is – among other things – a blatant abuse of the regulatory process, and it continues to inflict on Endo and Penwest grievous and irreparable harm. The seriousness of that harm is evidenced by the hundreds of millions of dollars in market capitalization that Endo and Penwest have lost because of Impax's conduct.

As a result, we request that you confirm on or before October 17, 2007 that (1) the initial submission of the ANDA referenced in your letter was not "substantially complete" and (2) Impax is withdrawing its Paragraph IV Notifications. We further request that, also on or before October 17, 2007, you explain the full basis for the FDA rescinding its acceptance of Impax's ANDA for substantive review and confirm the date on which Impax first learned that the FDA was rescinding its acceptance of Impax's ANDA.

In the event that Impax does not withdraw its Paragraph IV Notifications, we will need to proceed on a parallel track with the process for obtaining materials necessary to evaluate Impax's non-infringement claim. However, the Offer of Confidential Access you have proposed is unduly restrictive. First, we will require a complete copy of Impax's ANDA, as well as a samples (*i.e.*, 250-500 tablets for each dosage) of the material for which Impax is seeking approval. Second, in addition to outside counsel who are not engaged in patent prosecution, we will need to provide the confidential information to the following additional individuals: Caroline Manogue (Chief Legal Officer) and Robert Cobuzzi, Ph.D. (Senior Director Business Development) from Endo and Amale Hawi (Sr. Vice President, Pharmaceutical Development) from Penwest. In addition, we will need to discuss the evaluation of the confidential information in sufficient detail that the following members of management of Endo and Penwest can understand the basis of any conclusions: Peter Lankau (Chief Executive Officer), Nancy Wysenski (Chief Operating Officer), and Charles Rowland (Chief Financial Officer) for Endo and Jennifer Good (President & CEO) and Benjamin Palleiko (Sr. Vice President, Corporate Development & CFO) for Penwest. Third, the terms specifying application of California law and submission to the jurisdiction of California courts are unacceptable. We would be happy to discuss these issues with you at your convenience.

Finally, please be advised that in making the foregoing request for information and materials, Penwest and Endo do not admit that the Paragraph IV Notifications that have been sent to them by Impax are valid; to the contrary, our position, as stated more fully above, is that these Paragraph IV Notifications are null, void and without legal effect.

Regards,

Caroline B. Manogue
Chief Legal Officer
Endo Pharmaceuticals Inc.

_____

Benjamin Palleiko
Sr. Vice President, Corporate Development & CFO
Penwest Pharmaceuticals Co.

Dechert LLP

Princeton Pike Corporate Center
P.O. Box 5218
Princeton, NJ 08543-5218
+1 609 620 3200 Main
+1 609 620 3259 Fax
www.dechert.com

Delivery Address:
Princeton Pike Corporate Center
997 Lenox Drive, Building 3
Suite 210
Lawrenceville, NJ 08648-2317

ROBERT D. RHOAD

robert.rhoad@dechert.com
+1 609 620 3269 Direct
+1 609 873 9142 Fax

October 24, 2007

By Fax – (510) 476-2092
and First-Class Mail

Margaret Snowden
Vice-President, Intellectual Property
Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544

By Fax – (415) 397-7188
and First-Class Mail

Daralyn Durie, Esquire)
Keker & Van Nest LLP
710 Sansome Street
San Francisco, CA 94111

Re: Impax Laboratories, Inc.
Patent Certification Notice – U.S. Patent No. 7,276,250

Dear Ms. Snowden and Ms. Durie:

This firm represents Endo Pharmaceuticals, Inc. in connection Impax Laboratories, Inc.'s letter of October 2 providing notice that Impax had submitted ANDA 79-087, which includes a purported Paragraph IV notification with respect to the above-referenced patent. We are writing on behalf of both Endo and Penwest Pharmaceuticals Co. as a follow-up to their letter of October 17, 2007 to Impax in response to Impax's notice letter.

Endo and Penwest have not yet received any response to their October 17 letter. Accordingly, I called Impax today to follow-up on the letter, and in particular, to discuss Impax's offer of confidential access to its ANDA. This will confirm that I spoke with Ms. Snowden, who advised me that Impax had asked its outside counsel, Ms. Durie, to respond to our October 17 letter. I then called Ms. Durie, but was unable to reach her, and her voicemail message stated she would be out of the office until November 6. I then called Ms. Snowden back to advise her of that fact, and asked her to have Ms. Durie or someone else from her firm return my call. We ask that Impax provide its response to

our October 17 without delay, and that someone on behalf of Impax prepared to discuss Impax's offer of confidential access to its ANDA return my call as soon as possible.

In the meantime, in accordance with the terms of Impax's offer of confidential access to its ANDA and without waiver of the issues raised in our letter of October 17 and any objections we have to Impax's offer, we hereby give notice to Impax that Endo designates the following outside counsel that it has engaged in connection with this matter as "Authorized Evaluators" under the terms of Impax's offer: George G. Gordon, Thomas Lihan, Martin J. Black, Ann M. Caviani Pease, Robert D. Rhoad, and Lynn M. Terrebonne; and Penwest designates the following outside counsel that it has engaged in connection with this matter as "Authorized Evaluators" under the terms of Impax's offer: Robert Gunther, Lisa Pirozzolo, Michael Twomey and Christopher Noye. Each of the designated outside counsel for Endo is an attorney in the firm of Dechert LLP, and each of the designated outside counsel for Penwest Pharmaceuticals is an attorney in the firm of Wilmer Cutler Pickering Hale and Dorr LLP. None of the designated outside counsel are involved in patent prosecution matters either for Endo or Penwest.

Accordingly, we request that Impax send a confidential copy of the above-referenced ANDA, without delay, to the following designated outside counsel by overnight delivery at the listed addresses:

Ann Pease
Dechert LLP
2440 W. El Camino Real
Suite 700
Mountain View, CA 94040-1499

Lisa Pirozzolo
WilmerHale
60 State Street
Boston, MA 02109

Thank you in advance for your anticipated prompt attention to this matter.

Sincerely,

Robert D. Rhoad
RDR/wp

LAW OFFICES
KEKER & VAN NEST
LLP
710 SANSOME STREET
SAN FRANCISCO, CA 94111-1704
TELEPHONE (415) 391-5400
FAX (415) 397-7188
WWW.KVN.COM

DARALYN J. DURIE
DDURIE@KVN.COM

October 25, 2007

Robert D. Rhoad, Esq.
Dechert, LLC
Princeton Pike Corporate Center
997 Lenox Drive
Building 3, Suite 210
Lawrenceville, NJ 08648-2317

Dear Mr. Rhoad:

I represent Impax Laboratories, Inc.. I am in receipt of your letter regarding Impax's extended release oxymorphone hydrochloride product. As you are no doubt aware, the FDA initially accepted Impax's ANDA for extended release oxymorphone and then later rescinded that acceptance. We believe that the rescission was improper. We are taking steps to have the rescission reversed, and are confident that those efforts will be successful. We also believe that the PIV notice was proper, and we do not intend to withdraw it. With respect to your request regarding confidential access, you appear not to have signed the document. We are not inclined to modify it, but if you sign it, we will provide access to your Authorized Evaluators.

Very truly yours,

Daralyn J. Durie

DJD/dbm

405228.01

Petrow, Lois

From: Petrow, Lois
Sent: November 05 2007 4:32 PM
To: 'ABhansali@kvn.com'
Subject: Letter from George G. Gordon

Importance: High

Attachments: Document.pdf

Document.pdf (54 KB)

Please see attached letter from George G. Gordon, which has also been faxed to you this afternoon.

Lois I. Petrow, Secretary to George G. Gordon
Dechert LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104-2808
Direct: +1.215.994.2937
Fax: +1.215.994.2222
Lois.Petrow@dechert.com
www.dechert.com

Dechert LLP

Cira Centre
2929 Arch Street
Philadelphia, PA 19104-2808
+1 215 994 4000 Main
+1 215 994 2222 Fax
www.dechert.com

GEORGE G. GORDON

george.gordon@dechert.com
+1 215 994 2382 Direct
+1 215 655 2382 Fax

November 5, 2007

By Fax 415-397-7188
and Email

Asim M. Bhansali, Esquire
Keker & Van Nest LLP
710 Sansome Street
San Francisco, CA 94111

Re: Impax Laboratories, Inc.
Patent Certification Notices - U.S. Patent Nos. 5,662,933; 5,958,456; and 7,276,250

Dear Mr. Bhansali:

Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co. are in receipt of Impax's paragraph IV notice letters regarding the above-referenced patents. These notice letters, combined with Impax's announcement that the FDA rescinded initial acceptance of Impax's ANDA 79-087, raise several questions.

Please confirm whether the produced portions of ANDA 79-087 are from (1) the ANDA as originally filed, or (2) the ANDA as supplemented, amended or otherwise modified, other than by merely adding a paragraph IV certification. If the latter, please confirm that the produced portions are from the most recent ANDA submission made to the FDA and provide us with the corresponding portions from any other ANDA submissions made to the FDA, including the original ANDA, to the extent they differ. Please also advise us of any supplemental filings, amendments, or modifications concerning ANDA 79-087 since the date of filing, other than those merely adding a paragraph IV certification.

Also, please provide answers to the following questions:

Since the FDA's notice to Impax that it rescinded initial acceptance of Impax's ANDA 79-087, has the FDA notified Impax that ANDA 79-087 has been accepted for filing? If so, when was this notification made? Did the FDA accept the original ANDA 79-087? If not, did the FDA accept an ANDA that Impax had supplemented, amended, or otherwise modified in some manner other than merely adding a paragraph IV certification?

Dechert LLP

Has the FDA notified Impax that it has withdrawn, or intends to withdraw, its decision to rescind initial acceptance of Impax's ANDA 79-087? If so, when was this notification made?

We look forward to hearing from you on these issues.

Sincerely,

George G. Gordon

LAW OFFICES
KEKER & VAN NEST
LLP
710 SANSOME STREET
SAN FRANCISCO, CA 94111-1704
TELEPHONE (415) 391-5400
FAX (415) 397-7188

FACSIMILE TRANSMISSION COVER SHEET

November 7, 2007

To	Telephone	Facsimile
George Gordon Dechert LLP	(215) 994-2382	(215) 994-2222

From	Telephone	Code
Asim M. Bhansali	(415) 773-6608	6171/GAP

Re ***Abbott Laboratories, et al. v. Teva Pharmaceuticals, et al.***
USDC, Dist. of Delaware, Case No. 02-1512-KAJ

Number of Pages (Including Cover): 2

ORIGINAL WILL NOT FOLLOW THIS TRANSMISSION

COMMENTS

Please see attached correspondence.

Operator _____ Time Sent _____

IF YOU ENCOUNTER ANY DIFFICULTIES RECEIVING THIS TRANSMISSION, PLEASE CALL (415) 676-2277 OR (415) 391-5400

354205.01

LAW OFFICES
KEKER & VAN NEST
LLP
710 SANSOME STREET
SAN FRANCISCO, CA 94111-1704
TELEPHONE (415) 391-5400
FAX (415) 397-7188
WWW.KVN.COM

ASIM M. BHANSALI
ABHANSALI@KVN.COM

November 7, 2007

VIA FACSIMILE

George Gordon
Dechert LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104-2808

Re: Generic Oxymorphone ANDA

Dear Mr. Gordon:

I write in response to your letter of Monday, November 5.

In response to your first set of questions, I can say that no changes have been made to the parts of the ANDA that we disclosed to you. As I stated in my letter accompanying those excerpts from the ANDA, Impax believes those excerpts are sufficient for Endo and Penwest to determine that Impax does not infringe the patents for which a paragraph IV certification has been made.

In response to the second set of questions you posed regarding the issues surrounding the FDA's acceptance of Impax's ANDA, I can say that there have been no status changes since Daralyn Durie's letter to Robert Rhoad of October 25.

Sincerely,

ASIM M. BHANSALI

AMB/gap

EXHIBIT 8

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue Hayward, CA 94544
Phone (510) 476-2000 Fax (510) 476-2092

October 29, 2007

Via Certified Mail – Return Receipt Requested

Endo Pharmaceuticals Inc.
100 Endo Blvd.
Chadds Ford, PA 19317

Article # 70053110000157619446

Penwest Pharmaceuticals Co.
39 Old Ridgebury Rd., Suite 11
Danbury, CT 06810

Article # 70053110000157619453

Re: Patent Certification Notice – U.S. Patent Nos. 5,662,933 and 5,958,456
Oxymorphone Hydrochloride Extended-release Tablets
ANDA 79-087

To Whom It May Concern:

This is to provide the notice and information required by 21 U.S.C. §355(j)(2)(B)(i) and (ii) (§§ 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Impax Laboratories, Inc. ("Impax"), a Delaware corporation with its principal place of business at 30831 Huntwood Avenue, Hayward, California, 94544, has submitted an ANDA for the above-referenced drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certification with respect to U.S. Patent Nos. 5,662,933 and 5,958,456.

A detailed statement of the factual and legal bases for Impax's position regarding these patents is provided herein. Impax reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patents are invalid, unenforceable, or not infringed.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice-President, Regulatory Affairs and Compliance

MCS/aks

Enclosure: Impax Laboratories, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patent Nos. 5,662,933 and 5,958,456 Are Invalid, Unenforceable Or Not Infringed

CONFIDENTIAL

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NOS. 5,662,933 AND 5,958,456 ARE NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

This is the detailed statement of Impax Laboratories, Inc. ("Impax"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal basis for Impax's opinion that U.S. Patent Nos. 5,662,933 and 5,958,456 are invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, importation, use or sale of Impax's Oxymorphone HCl Extended Release 5 mg, 10 mg, 20 mg, and 40 mg tablets ("Impax Oxymorphone ER"), for which this detailed statement is submitted. Impax's factual and legal bases are set forth below.

I. Applicable Legal Standards

A U.S. patent gives the owner the right to preclude others from making, using or selling the invention defined by the claims of the patent in the United States and its territories for the term of the patent.[1] Those making, using or selling an invention defined by the claims of a patent are said to be directly infringing the claims of the patent. The patent statute also describes remedies for contributory infringement and inducement of infringement.[2] For there to be indirect infringement by one party, there must be direct infringement by another party. Furthermore, the act of filing an ANDA with patent invalidity or non-infringement certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) may create a cause of action for patent infringement.[3]

Evaluating infringement is a two-step process. First, the scope of the claims is determined, and second, the accused product or process is compared to the properly interpreted claims. The claims, properly construed as a matter of law by the court,[4] are the measure of the grant of the exclusive right to the patentee, and set out the metes and bounds of the invention.[5]

Claim construction may involve the use of both intrinsic and extrinsic evidence; however, the Federal Circuit in an *en banc* decision stressed the importance of giving the appropriate

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[1] 35 U.S.C. § 271(a).

[2] 35 U.S.C. § 271(b) & (c).

[3] 35 U.S.C. § 271(e)(2)(A).

[4] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995)(*en banc*), *aff'd*, 517 U.S. 370 (1996); *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

[5] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004).

weight to such evidence.[6] In particular, the Federal Circuit has instructed trial courts that as a starting point, claim terms are to be given their ordinary and customary meaning as understood by one of ordinary skill in the art.[7] In determining the ordinary and customary meaning, the trial court must first consider the claim term not only in the context of the particular claim, but also in the context of the rest of the claims, the specification, and the prosecution history.[8]

Once the language of the claims is properly interpreted, the claims must be "read on" the accused structure to determine whether each of the limitations recited in the claim is present.[9] Under the "all-elements" rule, a claim is not infringed unless each element of the claim, or a substantial equivalent of that element, is found in the accused device[10] When any limitation recited in a claim is not met, literal infringement is avoided.[11]

The absence of literal infringement does not necessarily mean that a process or device does not infringe a patent. The judicially created "doctrine of equivalents" allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes.[12] Thus, even though the language of a claim cannot be read literally upon a process or device, a claim can be infringed if the process or device "performs substantially the same function in substantially the same way to obtain the same result."[13] What constitutes "equivalency" must be determined against the context of the patent, the prior art, and the particular circumstances of the case.

---

[6] *Phillips v. AWH Corp. et al.*, 415 F.3d 1303 (Fed. Cir. 2005)(*en banc*).

[7] *Innova*, 381 F.3d at 1116; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

[8] *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005); *Vitronics*, 90 F.3d at 1582-83 (Fed. Cir. 1996).

[9] *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989).

[10] *Pennwalt Corp. v. Durand-Wayland Co.*, 833 F.2d 931, 935, (Fed. Cir. 1987); *Corning Glass Works*, 868 F.2d at 1259.

[11] *Lemelson v. United States*, 752 F.2d 1538 (Fed. Cir. 1985). See also, *Cooper Cameron Corp. v. Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317 (Fed. Cir. 2002).

[12] *Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. et al.*, 535 U.S. 722, 723 (2002).

[13] *Graver Tank & Mfg. Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). See also *Jonnson v. Stanley Works*, 711 F. Supp. 1395, 1407 (N.D. Ohio, 1989), *aff'd*, 903 F.2d 812 (Fed. Cir. 1990); *Fantasy Sports Properties, Inc. v. SportsLine.com, Inc.*, 287 F.3d 1108 (Fed. Cir. 2002).

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NOS. 5,662,933 AND 5,958,456 ARE NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

A patent and each of its issued claims is presumed to be valid.[14] Proof of invalidity of a patent or its claims is a complete defense to a charge of infringement of the claims of that patent. The claims of a patent can be found to be invalid under 35 U.S.C. §102 as anticipated or under §103 because they are obvious in light of the prior art. With respect to patent claim invalidity, "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."[15] The "combination of familiar elements according to known methods" is likely be obvious when it yields predictable results, and common sense, not a "formalistic conception of the words teaching, suggestion, and motivation" should guide obviousness analysis.[16] Factors to be considered in determining obviousness include the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the art, and secondary considerations.[17]

A patent application must describe how to make and use the invention in such full, clear, concise and exact terms as to enable any person of ordinary skill in the art to which it pertains to make and use the same.[18] For a claim to be enabled, the disclosure must be sufficiently described as to enable one of ordinary skill in the art to practice the invention without undue experimentation. A patent can be enabled even if it requires some experimentation to practice the invention: what is proscribed is undue experimentation.

Furthermore, the specification must be enabled at the time of filing the application, and a later filed publication cannot supplement an insufficient disclosure to render it enabling.[19] Later filed publications can be considered as evidence of the level of ordinary skill in the art at the time of filing the application, reinforcing the standard that the issue is whether one skilled in the art would have believed the application to be enabled at the time of filing. *In re Wands* set out 8 factors to be considered for enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill in the art, (5) the level of predictability in the art, (6) the amount of direction provided in the application, (7) the existence

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[14] 35 U.S.C. § 282.

[15] 35 U.S.C. § 103(a).

[16] *KSR Int'l Co. v. Teleflex Inc., et al.*, 127 S.Ct. 1727, 1739-41 (2007).

[17] *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

[18] *See* 35 U.S.C. §112, 1st paragraph.

[19] *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

of working examples in the specification, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.[20]

In order for a claim to be patentable, it also must meet the written description requirements of 35 U.S.C. § 112, Paragraph 1. The goals of the written description requirement are to (1) convey to the public what was invented, (2) put the public in possession of what the applicant claims as the invention, and (3) prevent an applicant from claiming subject matter that was not described in the specification as filed. As stated by the Federal Circuit, "compliance with [the] § 112 [written description requirement] has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing."[21] Possession of the invention is shown by describing the invention with specificity such as by words, structures, figures, diagrams, and formulas.[22]

The second paragraph of §112 requires the specification of a patent to "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[23] To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim.[24] Moreover, claims need not "be plain on their face in order to avoid condemnation for indefiniteness; rather, what [the Federal Circuit Court has] asked is that the claims be amenable to construction, however difficult that task may be."[25]

Furthermore, a patent may be rendered unenforceable for inequitable conduct. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith, and honesty.'"[26] "To hold a patent unenforceable due to inequitable conduct, there must be clear and convincing evidence that the applicant (1) made an affirmative misrepresentation or material fact, failed to disclose material information, or submitted false

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[20] *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

[21] *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1259 (Fed. Cir. 2004).

[22] Revised Interim Written Description Guidelines, available at <http://www.uspto.gov/web/menu/written.pdf>.

[23] *See* 35 U.S.C. § 112, 2nd paragraph.

[24] *Miles Lab. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[25] *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[26] *Ferring B.V. v. Barr Labs,* 437 F.3d 1181, 1186-87 (Fed. Cir. 2006) (quoting *Warner-Lambert Co. v. Teva Pharms. USA, Inc.,* 418 F.3d 1326, 1342 (Fed. Cir. 2005)).

material information, and (2) intended to deceive the [PTO]."[27] Intent need not, and rarely can, be proven by direct evidence.[28] "[I]n the absence of a credible explanation, intent to deceive *is generally inferred* from the facts and circumstances surrounding a knowing failure to disclose material information."[29] Further, the Federal Circuit recently "made it clear that 'a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead.'"[30]

II. U.S. Patent No. 5,662,933

U.S. Patent No. 5,662,933 ("the '933 patent") entitled "Controlled Release Formulation (Albuterol)" was filed on November 3, 1995 and issued on September 2, 1997. The '933 patent is a continuation-in-part application of Serial No. 08/118,924, filed September 9, 1993. The '933 patent is assigned to Edward Mendell Co., Inc. of Patterson, New York.

A. The Claims of the '933 patent

There are 48 claims issued in the '933 patent, which read as follows:

> 1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising: a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament; a sustained release excipient comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of reciprocally cross-linking when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid and a pharmaceutically acceptable hydrophobic material.

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[27] *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007).

[28] *Merck & Co., Inc. v. Danbury Pharmacal, Inc.* 873 F.2d 1418, 1422 (Fed. Cir. 1989).

[29] *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

[30] *Ferring*, 437 F.3d at 1191 (quoting *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997)).

2. The controlled release solid dosage form according to claim 1 wherein said diluent is a saccharide selected from the group consisting of sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

3. The controlled release solid dosage form according claim 1, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

4. The controlled release solid dosage form according claim 2, wherein said xanthan gum and said locust bean gum are present in about a 1:1 ratio, respectively, by weight.

5. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

6. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate and a polyvinyl acetate polymer.

7. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form.

8. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

9. The controlled release solid dosage form according to claim 1 wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

10. The controlled release solid dosage form according to claim 1 which is a tablet.

11. The controlled release solid dosage form according to claim 1 which is in granular form.

12. The controlled release solid dosage form according to claim 11, which comprises a gelatin capsule containing a sufficient amount of said granules to provide an effective dose of said therapeutically active medicament.

13. The controlled release solid dosage form according to claim 9, wherein said hydrophobic material is selected from the group consisting of carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, and mixtures of any of the foregoing, prior to incorporation of said medicament, said hydrophobic material being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

14. The controlled release solid dosage form according to claim 12 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

15. The controlled release solid dosage form according to claim 1 which comprises a granulation which is coated with a hydrophobic material to a weight gain from about 1% to about 20%.

16. The controlled release solid dosage form according to claim 14, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

17. The controlled release solid dosage form according to claim 16 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

18. The controlled release solid dosage form according to claim 17, wherein said mixture of sustained release excipient and medicament are coated with a hydrophobic material prior to tableting.

19. The controlled release solid dosage form according to claim 1 which is a tablet, said tablet further comprising a coating containing from about 10 to about 40 percent of the total amount of said medicament included in said dosage form.

20. The controlled release solid dosage form according to claim 1 wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

21. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament thereto, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

22. The method of claim 21, further comprising tableting said mixture of said sustained release excipient and said medicament.

23. The method of claim 21, further comprising coating said tablets with a hydrophobic coating to a weight gain from about 1% to about 20%.

24. The method of claim 21, further comprising granulating said sustained release excipient with a hydrophobic material.

25. The method of claim 21, wherein said medicament is albuterol or a salt or derivative thereof.

26. The method of claim 21, wherein said hydrophobic coating comprises ethylcellulose.

27. The method of claim 25, wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

28. The method of claim 21, wherein said sustained release excipient comprises from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent.

29. The method of claim 21, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 24 hours.

30. The method of claim 21, further comprising compressing the mixture of said sustained release excipient and said tablet into tablets.

31. The method of claim 21, wherein said medicament comprises a therapeutically effective dose of albuterol or salts and derivatives of the same.

32. A method of treating a patient with albuterol comprising, preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a albuterol, or a salt or derivative thereof, to said sustained release excipient, such that a final product is obtained having a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of albuterol for at least 12 hours. adding an amount of albuterol effective to render a desired therapeutic effect; tableting the resultant mixture such that a final product is obtained having a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol; and administering said tablet to a patient at a predetermined dosage interval from about 12 to about 24 hours.

33. The method of claim 32, further comprising coating said tablets with a hydrophobic material to a weight gain from about 1% to about 20%.

34. The method of claim 32, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

35. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 89 to about 150 (ng-hours/ml).

36. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 57 to about 157 (ng-hours/ml).

37. The controlled release solid dossage form of claim 1 which, when orally administered to a fed patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 75 to about 162 (ng-hour s/ml).

38. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a mean peak plasma concentration ranging from about 7 to about 12 ng/ml.

39. The controlled release solid dossage form of claim 1 which, when orally administered to a fasting patient, provides a mean peak plasma concentration ranging from about 4.5 to about 19 ng/ml.

40. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a mean peak plasma concentration ranging from about 6 to about 16 ng/ml.

41. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a time to mean peak plasma concentration ranging from about 3 to about 10 hours.

42. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a time to mean peak plasma concentration ranging from about 3 to about 6 hours.

43. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a time to mean peak plasma concentration ranging from about 3 to about 8 hours.

44. The controlled release solid dosage form of claim 35 wherein the area under the plasma concentration curve, to infinity, ranges from about 112 to about 129 (ng-hours/ml).

45. The controlled release solid dosage form of claim 38 wherein the mean peak plasma concentration ranges from about, 9.5 to about 12 ng.

46. The controlled release solid dosage form of claim 42 wherein the time to mean peak plasma concentration ranges from about 3.5 to about 8 hours.

47. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein time to peak plasma concentration in a fasted patient divided by a time to peak plasma concentration in a fed patient ranges from about 0.50 to about 0.70.

48. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein peak plasma concentration in a fasted patient divided by peak plasma concentration in a fed patient ranges from about 0.90 to about 1.10.

B. No Infringement of the Claims of the '933 patent

The '933 patent contains only 3 independent claims. Each of the independent claims 1, 21, and 32 of the '933 patent contains the specific limitation that the composition must include, among other ingredients, a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, in a ratio of about 1:3 to 3:1. Specifically, the composition of claim 1 requires "a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of reciprocally cross-linking when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to 3:1." The compositions of claims 21 and 32 require "about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to 3:1." Because each remaining claim contains the limitations of the independent claim from it depends, all of the claims in the '933 patent require the presence of a homopolysaccharide gum as a distinct ingredient from the heteropolysacharide gum, in the respective amounts claimed, for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claim of the '933 patent because Impax Oxymorphone ER does not contain a homopolysaccharide gum. Furthermore, the Impax Oxymorphone ER does not contain any equivalent to the homopolysaccharide gum claimed in the '933 patent.

Additionally, claims 9, 13, 20, 25, 27, and 31-34 contain the specific limitation that those compositions must also include albuterol. The Impax Oxymorphone ER does not literally infringe any of claims 9, 13, 20, 25, 27, or 31-34 of the '933 patent because Impax Oxymorphone ER does not contain albuterol. Furthermore, the Impax Oxymorphone ER does not contain any equivalent to the albuterol claimed in the '933 patent.

Therefore, for at least the reasons stated above, U.S. Patent No. 5,662,933 is not infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER.

IMPAX LABORATORIES, INC.'S DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES THAT U.S. PATENT NOS. 5,662,933 AND 5,958,456 ARE NOT INFRINGED BY THE MANUFACTURE, USE OR SALE OF IMPAX'S OXYMORPHONE HCl EXTENDED RELEASE 5 mg, 10 mg, 20 mg, and 40 mg TABLETS

III. U.S. Patent No. 5,958,456

U.S. Patent No. 5,958,456 ("the '456 patent") entitled "Controlled Release Formulation (Albuterol)" was filed on July 1, 1997 and issued on September 28, 1999. The '456 patent is a continuation application of Serial No. 08/533,088, filed November 3, 1995. The '456 patent is assigned to Edward Mendell Co., Inc. of Patterson, New York.

A. The Claims of the '456 patent

There are 16 claims issued in the '456 patent, which read as follows:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising: a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament; a sustained release excipient comprising a gelling agent; a pharmaceutically acceptable hydrophobic material; and an inert pharmaceutical diluent wherein the ratio of said inert diluent to said gelling agent is from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid.

2. The controlled release solid dosage form according to claim 1 wherein said inert diluent is selected from the group consisting of pharmaceutically acceptable saccharides, polyhydric alcohols, pre-manufactured direct compression diluents, and mixtures of any of the foregoing.

3. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

4. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

5. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25 percent to about 50 percent, by weight, of the solid dosage form.

6. The controlled release solid dosage form according to claim 1, wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

7. The controlled release solid dosage form according to claim 1 which is a tablet.

8. The controlled release solid dosage form according to claim 1, which is in granulate form.

9. The controlled release solid dosage form according to claim 8, wherein said granulate is coated with a hydrophobic material to a weight gain from about 1 percent to about 20 percent.

10. The controlled release solid dosage form according to claim 1, wherein the medicament comprises an amount of albuterol equivalent to about 4 mg to about 16 mg of albuterol free base.

11. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising preparing of a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent, from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to about 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and adding a therapeutically effective amount of a medicament to said excipient, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

12. The method of claim 11, further comprising compressing said mixture of said sustained release excipient and said medicament into tablets.

13. The method of claim 11, wherein said medicament is albuterol or a salt or derivative thereof.

14. The method of claim 13, further comprising coating the resultant tablets with a hydrophobic coating to a weight gain from about 1 percent to about 20 percent.

15. A method of treating a patient with albuterol comprising: preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of albuterol or a salt or derivative thereof to said sustained release excipient, tableting the resultant mixture into tablets such that said tablets have a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol for at least 12 hours; and administering said tablet to a patient on a once-a-day or twice-a-day basis.

16. The method of claim 15, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

B. No Infringement of the Claims of the '456 patent

The '456 patent contains only 3 independent claims. Each of the independent claims 1, 11, and 15 of the '456 patent have the limitation that the composition must contain the separate component "a pharmaceutically acceptable hydrophobic material" among other ingredients. Specifically, the composition of claim 1 comprises "a pharmaceutically acceptable hydrophobic material." The composition of claims 11 and 15 comprise "from about 1 to 90 percent by weight of a pharmaceutically acceptable hydrophobic material." Because each remaining claim contains the limitations of the independent claim from which it depends, all dependent claims in the '456 patent require either "a pharmaceutically acceptable hydrophobic material" or "from about 1 to

90 percent by weight of a pharmaceutically acceptable hydrophobic material" for a finding of infringement.

The Impax Oxymorphone ER does not literally infringe any claim of the '456 patent because Impax Oxymorphone ER does not contain a "pharmaceutically acceptable hydrophobic material" as defined and claimed in the '456 patent. Furthermore, the Impax Oxymorphone ER does not contain any equivalent to the pharmaceutically acceptable hydrophobic material as defined and claimed in the '456 patent.

Additionally, claims 6, 10, 13, and 15-16 contain the specific limitation that those compositions must also include albuterol. The Impax Oxymorphone ER does not literally infringe any of claims 6, 10, 13, and 15-16 of the '456 patent because Impax Oxymorphone ER does not contain albuterol. Furthermore, the Impax Oxymorphone ER does not contain any equivalent to the albuterol claimed in the '456 patent.

Therefore, for at least the reasons stated above, U.S. Patent No. 5,958,456 is not infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER.

IV. Conclusion

For the reasons stated above, none of the claims of U.S. Patent Nos. 5,662,933 or 5,958,456 are infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Impax Oxymorphone ER. Impax reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable or not infringed.

EXHIBIT 9

Press Release

IMPAX Comments on Lawsuit Related to Generic Version of Opana(R) ER

HAYWARD, Calif.--(BUSINESS WIRE)--Nov. 19, 2007--IMPAX Laboratories, Inc. (OTC:IPXL) today confirmed that Endo Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. have filed a lawsuit against the Company in the United States District Court for the District of Delaware alleging patent infringement related to IMPAX's filing of an Abbreviated New Drug Application (ANDA) with the U.S. Food and Drug Administration (FDA) for oxymorphone hydrochloride extended-release tablets CII, a generic version of Opana(R) ER.

IMPAX's submission includes a Paragraph IV certification stating the Company believes its product does not infringe U.S. Patent Nos. 7,276,250, 5,662,933 and 5,958,456 or that the patents are invalid or unenforceable. The suit alleges infringement of U.S. Patent Nost. 5,662,933 and 5,958,456 and also seeks declaratory judgment that the court to declare that the Paragraph IV Certification Notices that IMPAX served on Endo and Penwest are null, void and of no legal effect and that, therefore, the Court has no subject matter jurisdiction over the patent infringement claims.

"We believe that our Paragraph IV certification for generic Opana ER was proper, that our product does not infringe any valid, enforceable patent, and, as such, we will vigorously defend this lawsuit. Furthermore, we believe that the rescission of our ANDA by the FDA was inappropriate and we are continuing to work with the FDA to allow our ANDA to stand," said Larry Hsu, Ph.D., president and chief executive officer of IMPAX Laboratories.

Endo Pharmaceuticals Holdings Inc. and Penwest Pharmaceuticals Co. manufacture and market Opana ER for the treatment of moderate to severe pain. According to Wolters Kluwer Health, U.S. sales of Opana ER tablets were approximately $48.8 million in the 12 months ended September 30th, 2007.

About IMPAX Laboratories, Inc.

IMPAX Laboratories, Inc. is a technology based specialty pharmaceutical company applying its formulation expertise and drug delivery technology to the development of controlled-release and specialty generics in addition to the development of branded products. IMPAX markets its generic products through its Global Pharmaceuticals division and markets its branded products through the IMPAX Pharmaceuticals division. Additionally, where strategically appropriate, IMPAX has developed marketing partnerships to fully leverage its technology platform. IMPAX Laboratories is headquartered in Hayward, California, and has a full range of capabilities in its Hayward and Philadelphia facilities. For more information, please visit the Company's Web site at: www.impaxlabs.com.

"Safe Harbor" statement under the Private Securities Litigation Reform Act of 1995:

To the extent any statements made in this news release contain information that is not historical, these statements are forward-looking in nature and express the beliefs and expectations of management. Such statements are based on current expectations and involve a number of known and unknown risks and uncertainties that could cause IMPAX's future results, performance or achievements to differ significantly from the results, performance or achievements expressed or implied by such forward-looking statements. Such risks and uncertainties include, but are not limited to, possible adverse effects resulting from the delisting of and suspension of trading in IMPAX's stock, the SEC proceeding to determine whether to suspend or revoke the registration of IMPAX's securities under section 12 of the Securities Exchange Act, IMPAX's delay in filing its 2004 Form 10-K, its Form 10-Q for each of the first three quarters of 2005, 2006, and 2007, its Form 10-K for 2005 and 2006, the actual time that will be required to complete the filing of IMPAX's delinquent periodic reports, IMPAX's ability to obtain sufficient capital to fund its operations, the difficulty of predicting FDA filings and approvals, consumer acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, IMPAX's ability to successfully develop and commercialize pharmaceutical products, IMPAX's reliance on key strategic alliances, the uncertainty of patent litigation, the availability of raw materials, the regulatory environment, dependence on patent and other protection for innovative products, exposure to product liability claims, fluctuations in operating results and other risks detailed from time to time in IMPAX's filings with the Securities and Exchange Commission. Forward-looking statements speak only as to the date on which they are made, and IMPAX undertakes no obligation to update publicly or revise any forward-looking statement, regardless of whether new information becomes available, future developments occur or

otherwise.

CONTACT: IMPAX Laboratories, Inc.
Larry Hsu, Ph.D. President & CEO
510-476-2000, Ext. 1111
Arthur Koch, CFO
215-933-0351
www.impaxlabs.com
or
Investor Relations Contacts:
Lippert/Heilshorn & Associates, Inc.
Kim Sutton Golodetz, 212-838-3777
kgolodetz@lhai.com
Bruce Voss, 310-691-7100
bvoss@lhai.com
www.lhai.com

SOURCE: IMPAX Laboratories, Inc.

EXHIBIT 10

Paragraph IV Patent Certifications As of November 16, 2007

Below is a list of drug products for which an Abbreviated New Drug Application (ANDA) has been received by the Office of Generic Drugs (OGD) containing a "Paragraph IV" patent certification. This list includes the name of the drug product, dosage form, strength (subject of Paragraph IV certification), reference listed drug (RLD), **and the date on which the first substantially complete generic drug application was submitted to the Agency (on a prospective basis beginning 3/2/04)**. The Agency will not disclose the identity of the applicant. This information will be updated twice a month and will be as current as the last update. This information should be used for reference only. The Agency will make every effort to ensure the accuracy of the information disclosed in this list. However, any discrepancies or disparities should be discussed with the Regulatory Support Branch at 301-827-5862, before making any decisions based on this information.

Any additions from the preceding list are marked with the New!! icon.

- FDA News: FDA announces measure to improve generic drug access
- Docket # 2000P-1556 Policy regarding ANDA holder confidentiality

DRUG NAME	DOSAGE FORM	STRENGTH	RLD	DATE OF SUBMISSION
Acarbose	Tablets	25 mg, 50 mg and 100 mg	Precose	3/22/2005
Acetaminophen	Extended-release Tablets	650 mg	Tylenol	
Acetaminophen/ Aspirin/ Caffeine	Tablets	250 mg/250 mg/ 65 mg	Excedrin (migraine)	
Acetaminophen and Tramadol Hydrochloride	Tablets	325 mg/ 37.5 mg	Ultracet	
Acyclovir Sodium	Injection	50 mg/mL, 10 mL and 20 mL vials	Zovirax	
Adenosine	Injection	3 mg/mL, 20 mL and 30 mL vials	Adenoscan	4/18/2005
Albuterol Sulfate	Oral Syrup	2 mg(base)/ 5 mL	Ventolin	
Albuterol Sulfate	Extended-release Tablets	4 mg and 8 mg	Volmax	
Albuterol Sulfate	Inhalation	0.021% and	Accuneb	10/19/2005

	Solution	0.042%		
Albuterol Sulfate/ Ipratropium Bromide	Inhalation Solution	0.083%/ 0.017%	Duoneb	
Alendronate Sodium New!!	Oral Solution	70 mg/75 mL	Fosamax	9/7/2007
Alendronate Sodium	Tablets	5 mg, 10 mg, 35 mg, 40 mg and 70 mg	Fosamax	
Alfuzosin Hydrochloride	Extended-release Tablets	10 mg	Uroxatral	6/12/2007
Alprazolam	Orally Disintegrating Tablets	0.25 mg, 0.5 mg, 1 mg and 2 mg	Niravam	12/27/2005
Alprazolam	Tablets	0.25 mg, 0.5 mg, 1 mg and 2 mg	Xanax	
Almotriptan Malate	Tablets	6.25 mg and 12.5 mg	Axert	12/8/2005
Amifostine	For Injection	500 mg/vial	Ethyol	4/16/2004
Amlodipine Besylate	Tablets	2.5 mg, 5 mg and 10 mg	Norvasc	
Amlodipine Besylate and Atorvastatin Calcium Tablets	Tablets	5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg	Caduet	12/29/2006
Amlodipine Besylate and Benazepril Hydrochloride	Capsules	2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg and 10 mg/20 mg	Lotrel	6/9/2004
Amlodipine Besylate and Benazepril Hydrochloride	Capsules	5 mg/40 mg and 10 mg/40 mg	Lotrel	11/17/2006
Argatroban New!!	Injection	100 mg/mL, 2.5 mL vials	Argatroban	9/24/2007
Aripiprazole	Tablets	2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg	Abilify	11/15/2006
Aripiprazole	Orally Disintegrating Tablets	10 mg, 15 mg, 20 mg and 30 mg	Abilify	11/15/2006
Aspirin and Dipyridamole	Extended-release Capsules	25 mg and 200 mg	Aggrenox	2/1/2007
Atenolol	Tablets	25 mg, 50 mg and 100 mg	Tenormin	
Atenolol/ Chlorthalidone	Tablets	50 mg/25 mg and 100 mg/25 mg	Tenoretic	

Atomoxetine Hydrochloride	Capsules	10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg	Strattera	5/29/2007
Atorvastatin Calcium	Tablets	10 mg, 20 mg, 40 mg and 80 mg	Lipitor	
Azelastine Hydrochloride	Nasal Spray	0.125 mg base/spray	Astelin	11/14/2005
Azelastine Hydrochloride	Ophthalmic Solution	0.05%	Optivar	12/13/2006
Betamethasone Valerate	Foam	0.12%	Luxiq	8/10/2007
Betaxolol	Ophthalmic Solution	0.5%(base)	Betoptic	
Brimonidine Tartrate	Ophthalmic Solution	0.1%	Alphagan P	12/20/2006
Brimonidine Tartrate	Ophthalmic Solution	0.15%	Alphagan P	11/03/2006
Brimonidine Tartrate	Ophthalmic Solution	0.2%	Alphagan	
Budesonide	Inhalation Suspension	0.25 mg/2 mL and 0.5 mg/2 mL	Pulmicort Respules	9/15/2005
Budesonide	Nasal Spray	0.032 mg (32 mcg)/spray	Rhinocort	5/14/2007
Bupropion Hydrochloride	Extended-release Tablets	100 mg, 150 mg and 200 mg	Wellbutrin SR	
Bupropion Hydrochloride	Extended-release Tablets	150 mg	Zyban	
Bupropion Hydrochloride	Extended-release Tablets	150 mg and 300 mg	Wellbutrin XL	9/21/2004
Bupropion Hydrochloride	Tablets	75 mg and 100 mg	Wellbutrin	
Buspirone Hydrochloride	Tablets	5 mg, 7.5 mg, 10 mg, 15 mg and 30 mg	Buspar	
Butorphanol Tartrate	Nasal Spray	10 mg/mL	Stadol NS	
Calcipotriene	Topical Solution	0.005%	Dovonex	5/19/2006
Calcitonin-Salmon	Nasal Spray	200 IU/spray	Miacalcin	
Calcitonin-Salmon (Recombinant)	Nasal Spray	200 IU/spray	Fortical	3/29/2006
Calcitriol	Injection	1 mcg/mL and 2 mcg/mL, 1 mL vials	Calcijex	
Calcium Acetate	Capsules	EQ 169 mg calcium	PhosLo	5/31/2005
Calcium Carbonate/	Chewable	800 mg/ 10	Pepcid	11/1/2004

Famotadine/ Magnesium Hydroxide	Tablets	mg/ 165 mg (OTC)	Complete	
Candesartan Cilexetil	Tablets	4 mg, 8 mg, 16 mg and 32 mg	Atacand	12/22/2006
Captopril	Tablets	12.5 mg, 25 mg, 50 mg, and 100 mg	Capoten	
Carbamazepine	Extended-release Capsules	100 mg and 200 mg	Carbatrol	2/2/2006
Carbamazepine New!!	Extended-release Capsules	200 mg and 300 mg	Equetro	8/21/2007
Carbamazepine	Extended-release Capsules	300 mg	Carbatrol	
Carbamazepine	Extended-release Tablets	100 mg	Tegretol-XR	12/30/2005
Carbamazepine	Extended-release Tablets	200 mg and 400 mg	Tegretol-XR	
Carbidopa/ Levodopa	Extended-release Tablets	25 mg/100 mg and 50 mg/200 mg	Sinemet CR	
Carbidopa, Levodopa and Entacapone	Tablets	25/100/200 mg and 37.5/150/200 mg	Stalevo 100 and Stalevo 150	6/29/2007
Carboplatin	For Injection	50 mg/vial, 150 mg/vial and 450 mg/vial	Paraplatin	
Carboplatin	Injection	50 mg/vial, 150 mg/vial and 450 mg/vial	Paraplatin	
Carisoprodol/ Aspirin	Tablets	200 mg/ 325 mg	Soma Compound	
Carisoprodol/ Aspirin/ Codeine	Tablets	200 mg/ 325 mg/ 16 mg	Soma Compound with Codeine	
Carvedilol	Tablets	3.125 mg, 6.25 mg, 12.5 mg and 25 mg	Coreg	
Celecoxib	Capsules	100 mg, 200 mg and 400 mg	Celebrex	
Cetirizine HCL	Syrup	5 mg/5 mL	zyrtec	3/19/2007
Cetirizine Hydrochloride and Pseudoephedrine	Extended-release Tablets	5 mg/120 mg	Zyrtec-D	6/2/2004
Cetirizine Hydrochloride	Chewable	5 mg and 10	Zyrtec	3/25/2005

	Tablets	mg		
Chlorhexidine Gluconate	Scrub brush/sponge	4%	Hibiclens	
Chlorpheniramine Polistirex and Hydrocodone Polistirex	Extended-release Capsules	8 mg/10 mg and 4 mg/5 mg	Tussionex	9/10/2004
Ciclopirox	Gel	0.77%	Loprox	5/10/2006
Ciprofloxacin Hydrochloride	Tablets	100 mg, 250 mg, 500 mg and 750 mg	Cipro	
Cisplatin	Injection	1 mg/mL, 10 mL, 50 mL, 100 mL and 200 mL vials	Platinol-AQ	
Cisplatin	For Injection	10 mg/vial and 50 mg/vial	Platinol	
Clobetasol Propionate	Topical Foam	0.05%	Olux	6/27/2005
Clobetasol Propionate	Lotion	0.05%	Clobex	3/27/2006
Clonidine Hydrochloride	Transdermal System	0.1 mg/day, 0.2 mg/day, and 0.3 mg/day	Catapres-TTS	
Clopidogrel Bisulfate	Tablets	75 mg	Plavix	
Colestipol Hydrochloride	Tablets	1 g	Colestid	8/23/2005
Conjugated Estrogens	Tablets	0.3 mg and 0.625 mg	Premarin	
Cyclobenzaprine Hydrochloride	Tablets	10 mg	Flexeril	
Cyclophosphamide	For Injection	100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial and 2 g/vial	Cytoxan	
Desloratadine	Tablets	5 mg	Clarinex	6/21/2006
Desloratadine	Orally Disintegrating Tablets	2.5 mg and 5 mg	Clarinex	6/21/2006
Desloratadine and Pseudoephedrine Sulfate	Extended-release Tablets	2.5 mg/120 mg	Clarinex-D 24 Hour	6/1/2007
Desloratadine and Pseudoephedrine Sulfate	Extended-release Tablets	5 mg/240 mg	Clarinex-D 24 Hour	6/21/2006
Desmopressin Acetate	Injection	4 mcg/mL, 1 mL and 10 mL vials	DDAVP	
Desmopressin Acetate	Nasal Spray	0.01%	DDAVP	
Desmopressin Acetate	Tablets	0.1 mg and 0.2 mg	DDAVP	
Desogestrel; Ethinyl	Tablets	0.15mg/ 0.02	Mircette	

Estradiol Tablets		mg and 0.01 mg		
Dexmethylphenidate Hydrochloride	Tablets	2.5 mg	Focalin	7/27/2004
Dexmethylphenidate Hydrochloride	Tablets	5 mg and 10 mg	Focalin	5/27/2004
Dexmethylphenidate Hydrochloride	Extended-release Capsules	15 mg	Focalin XR	5/14/2007
Dexmethylphenidate Hydrochloride	Extended-release Capsules	5 mg, 10 mg and 20 mg	Focalin XR	3/30/2007
Dexrazoxane	For Injection	250 mg/vial	Zinecard	
Dextroamphetamine saccharate; Amphetamine aspartate; Dextroamphetamine Sulfate; Amphetamine Sulfate	Extended-release Capsules	5 mg, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg	Adderall XR	
Dextroamphetamine saccharate; Amphetamine aspartate; Dextroamphetamine Sulfate; Amphetamine Sulfate	Tablets	7.5 mg, 12.5 mg and 15 mg	Adderall	
Diazepam	Tablets	2 mg, 5 mg and 10 mg	Valium	
Diazepam	Rectal Gel	2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL and 20 mg/4 mL	Diastat	3/23/2004
Didanosine	Delayed-release Capsules	200 mg, 250 mg and 400 mg	Videx EC	6/1/2004
Diltiazem Hydrochloride	Extended-release Capsules	60 mg, 90 mg and 120 mg	Cardizem SR	
Diltiazem Hydrochloride	Extended-release Capsules	120 mg, 180 mg and 240 mg	Dilacor XR	
Diltiazem Hydrochloride	Extended-release Capsules	120 mg, 180 mg, 240 mg and 300 mg	Cardizem CD	
Diltiazem Hydrochloride	Extended-release Capsules	120 mg, 180 mg, 240 mg, 300 mg, 360 mg and 420 mg	Tiazac	
Diltiazem Hydrochloride	Extended-release Tablets	120 mg, 180 mg, 240 mg,	Cardizem LA	8/30/2005

		300 mg and 360 mg		
Diltiazem Hydrochloride	Extended-release Tablets	420 mg	Cardizem LA	4/25/2005
Divalproex Sodium	Delayed-release Tablets	125 mg, 250 mg and 500 mg	Depakote	
Divalproex Sodium	Extended-release Tablets	250 mg	Depakote ER	5/3/2004
Divalproex Sodium	Extended-release Tablets	500 mg	Depakote ER	2/8/2005
Donepezil Hydrochloride	Tablets	5 mg and 10 mg	Aricept	
Dorzolamide Hydrochloride	Ophthalmic Solution	2%	Trusopt	10/7/2005
Dorzolamide Hydrochloride and Timolol Maleate	Ophthalmic Solution	2%/0.5%	Cosopt	10/7/2005
Doxazosin Mesylate	Tablets	1 mg, 2 mg, 4 mg and 8 mg	Cardura	
Drospirenone and Ethinyl Estradiol	Tablets	3 mg/0.02 mg	Yaz	9/29/2006
Drospirenone and Ethinyl Estradiol	Tablets	3 mg/0.03 mg	Yasmin	1/7/2005
Enalapril Maleate	Tablets	2.5 mg, 5 mg, 10 mg and 20 mg	Vasotec	
Enoxaparin Sodium	Injection	100 mg/mL, 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes	Lovenox	
Enoxaparin Sodium	Injection	150 mg/mL, 0.6 mL, 0.8 mL and 1 mL prefilled syringes	Lovenox	
Enoxaparin Sodium	Injection	100 mg/mL, 3 mL vials	Lovenox	12/7/2006
Entacapone	Tablets	200 mg	Comtan	4/11/2007
Eplerenone	Tablets	25 mg and 50 mg	Inspra	9/27/2006
Escitalopram Oxalate	Capsules	5 mg	Lexapro	8/17/2005
Escitalopram Oxalate	Capsules	10 mg and 20 mg	Lexapro	3/30/2005
Escitalopram Oxalate	Tablets	5 mg, 10 mg and 20 mg	Lexapro	
Esmolol Hydrochloride	Injection	10 mg/mL, 10 mL vial	Brevibloc	

Esomeprazole Magnesium	Delayed-release Capsules	20 mg and 40 mg	Nexium	8/5/2005
Estradiol	Transdermal System	0.0375 mg/day and 0.06 mg/day	Climara	
Estradiol	Transdermal System	0.05 mg/day and 0.1 mg/day	Climara	9/12/2005
Estradiol; Estradiol and Norgestimate	Tablets	1 mg; 1 mg and 0.09 mg	Prefest	
Etodolac	Extended-release Tablets	400 mg, 500 mg and 600 mg	Lodine XL	
Ezetimibe	Tablets	10 mg	Zetia	10/25/2006
Famciclovir	Tablets	125 mg, 250 mg and 500 mg	Famvir	12/28/2004
Famotidine	Injection	10 mg/mL, 2 mL vials; unpreserved	Pepcid	
Famotidine	Injection	10 mg/mL, 4 mL and 20 mL vials; preserved	Pepcid	
Famotidine	Injection	10 mg/mL, 50 mL vial, pharmacy bulk package; unpreserved	Pepcid	
Famotidine	Tablets	10 mg (OTC)	Pepcid AC	
Famotidine	Tablets	20 mg and 40 mg	Pepcid	
Famotidine	Tablets (Chewable)	10 mg (OTC)	Pepcid AC (chewable)	
Felodipine	Extended-release Tablets	2.5 mg, 5 mg and 10 mg	Plendil ER	
Fenofibrate	Capsules	67 mg, 134 mg and 200 mg	Tricor	
Fenofibrate	Tablets	54 mg, 107 mg and 160 mg	Tricor	
Fentanyl	Transdermal Extended-release Film	0.6 mg/24 hr, 1.2 mg/ 24 hr, 1.8 mg/ 24 hr and 2.4 mg/ 24 hr	Duragesic	
Fentanyl Citrate	Lozenges	0.2 mg	Actiq	10/29/2004
Fentanyl Citrate	Lozenges	0.4 mg	Actiq	10/6/2004
Fentanyl Citrate	Lozenges	0.6 mg	Actiq	12/20/2004

Fentanyl Citrate	Lozenges	0.8 mg, 1.2 mg and 1.6 mg	Actiq	11/22/2004
Fexofenadine Hydrochloride	Capsules	60 mg	Allegra	
Fexofenadine Hydrochloride	Tablets	30 mg, 60 mg and 180 mg	Allegra	
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride	Extended-release Tablets	60 mg/120 mg	Allegra-D	
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride	Extended-release Tablets	180 mg/240 mg	Allegra-D 24 Hour	6/6/2007
Finasteride	Tablets	1 mg	Propecia	
Finasteride	Tablets	5 mg	Proscar	
Flecainide Acetate	Tablets	50 mg, 100 mg and 150 mg	Tambocor	
Fluconazole	For Oral Suspension	50 mg/5 mL and 200 mg/5 mL	Diflucan for Oral Suspension	
Fluconazole	Tablets	50 mg, 100 mg, 150 mg and 200 mg	Diflucan	
Flunisolide	Nasal Solution	0.025%	Nasalide	
Fluocinonide	Ointment	0.05%	Lidex	
Fluoxetine Hydrochloride	Tablets	10 mg and 20 mg	Prozac	
Fluoxetine Hydrochloride	Capsules	10 mg, 20 mg and 40 mg	Prozac	
Fluoxetine Hydrochloride	Delayed-release Capsules	90 mg	Prozac Weekly	
Fluoxetine Hydrochloride	Oral Solution	20 mg (base)/5 mL	Prozac	
Fluoxetine Hydrochloride	Capsules	10 mg and 20 mg	Sarafem	
Flutamide	Capsules	125 mg	Eulexin	
Fluvastatin Sodium	Extended-release Tablets	80 mg	Lescol XL	3/15/2007
Fosinopril Sodium	Tablets	10 mg, 20 mg and 40 mg	Monopril	
Fosinopril Sodium and Hydrochlorothiazide	Tablets	10 mg/12.5 mg and 20 mg/12.5 mg	Monopril HCT	
Gabapentin	Capsules	100 mg, 300 mg and 400 mg	Neurontin	
Gabapentin	Oral Solution	250 mg/5 mL	Neurontin	

Gabapentin	Tablets	100 mg, 300 mg and 400 mg	Neurontin	
Gabapentin	Tablets	600 mg and 800 mg	Neurontin	
Galantamine Hydrobromide	Extended-release Capsules	8 mg	Razadyne ER	3/2/2006
Galantamine Hydrobromide	Extended-release Capsules	16 mg and 24 mg	Razadyne ER	3/11/2006
Galantamine Hydrobromide	Tablets	4 mg, 8 mg and 12 mg	Razadyne	2/28/2005
Ganciclovir Sodium	Capsules	250 mg and 500 mg	Cytovene	
Gatifloxacin	Injection	10 mg/mL, 20 mL and 40 mL vials	Tequin	11/24/2004
Gatifloxacin	Ophthalmic Solution	0.3 %	Zymar	7/19/2007
Gatifloxacin	Tablets	200 mg and 400 mg	Tequin	
Gatifloxacin in Dextrose 5% in Plastic Container	Injection	2 mg/mL, 100 mL and 200 mL containers (plastic)	Tequin	12/13/2004
Gemcitabine	For Injection	200 mg/vial	Gemzar	11/1/2005
Gemcitabine	For Injection	1g/vial	Gemzar	11/14/2005
Gemcitabine New!!	For Injection	2 g/vial	Gemzar	8/24/2007
Glimepiride and Rosiglitazone Maleate	Tablets	1 mg/4 mg, 2 mg/4 mg and 4 mg/4 mg	Avandaryl	12/22/2006
Glipizide	Extended-release Tablets	2.5 mg, 5 mg and 10 mg	Glucotrol XL	
Glyburide	Tablets	1.5 mg, 3 mg, 4.5 mg and 6 mg	Glynase	
Glyburide/ Metformin Hydrochloride	Tablets	1.25mg/250 mg, 2.5 mg/500 mg and 5 mg/500 mg	Glucovance	
Granisetron Hydrochloride	Injection	0.1 mg/mL, 1 mL single dose vial	Kytril	3/8/2007
Granisetron Hydrochloride	Injection	1 mg/mL, 1 mL vials	Kytril	6/1/2004
Granisetron Hydrochloride	Injection	1 mg/mL, 4 mL multi-dose	Kytril	7/19/2004

		vials		
Guaifenesin*	Extended-release Tablets	600 mg and 1.2 gm	Mucinex	6/9/2006
Hydrocodone Bitartrate and Ibuprofen	Tablets	2.5 mg/200 mg	Vicoprofen	2/24/2006
Hydrocodone Bitartrate and Ibuprofen	Tablets	5 mg/200 mg	Vicoprofen	5/27/2005
Hydrocodone Bitartrate and Ibuprofen	Tablets	7.5 mg/200 mg	Vicoprofen	
Hydrocodone Bitartrate and Ibuprofen	Tablets	10 mg/200 mg	Vicoprofen	
Ibandronate Sodium	Injection	1 mg/mL, 3 mL Vial	Boniva	8/31/2007
Ibandronate Sodium	Tablets	2.5 mg and 150 mg	Boniva	5/16/2007
Ibuprofen	Oral Drops	40 mg/mL	Children's Motrin Drops	
Ibuprofen	Oral Suspension	50 mg/1.25 mL	Concentrated Motrin Infant Drops	6/29/2007
Ibuprofen	Oral Suspension	100 mg/5 mL (Rx)	Motrin	
Ibuprofen	Oral Suspension	100 mg/5 mL (OTC)	Children's Motrin	
Ibuprofen	Chewable Tablets	50 mg and 100 mg	Children's Motrin, Junior Strength Motrin	
Ibuprofen Potassium and Pseudoephedrine Hydrochloride	Capsules	200 mg/30 mg	Advil Cold and Sinus	12/27/2004
Ibuprofen and Pseudoephedrine Hydrochloride	Oral Suspension	100 mg/ 15 mg per 5 mL	Children's Motrin Cold	
Ibuprofen and Pseudoephedrine Hydrochloride	Tablets	200 mg/30 mg	Advil Cold and Sinus	
Ifosfamide	For Injection	1 g/vial and 3 g/vial	Ifex	
Ifosfamide	Injection	50 mg/mL, 20 mL vials and 60 mL vials	Ifex	
Ifosfamide/ Mesna	For Injection/ Injection Kit	1 g/vial; 100 mg/mL, 10 mL vials and 3 g/vial; 100 mg/mL, 10 mL vials	Ifex/ Mesnex Kit	
Ifosfamide/ Mesna	Injection/	50 mg/mL, 20	Ifex/ Mesnex	

	Injection Kit	mL and 60 mL vials; 100 mg/mL, 10 mL vial	Kit	
Imatinib Mesylate	Tablets	100 mg and 400 mg	Gleevec	3/12/2007
Imiquimod	Cream	5%	Aldara	10/17/2006
Indomethacin	Extended-release Capsules	75 mg	Indocin SR	
Irbesartan	Tablets	75 mg, 150 mg and 300 mg	Avapro	5/25/2004
Irbesartan and Hydrochlorothiazide	Tablets	150 mg/12.5 mg and 300 mg/12.5 mg	Avalide	11/10/2004
Irbesartan and Hydrochlorothiazide	Tablets	300 mg/25 mg	Avalide	6/6/2006
Irinotecan Hydrochloride	Injection	20 mg/mL, 2 mL and 5 mL vials	Camptosar	7/26/2004
Itraconazole	Capsules	100 mg	Sporanox	
Ketoprofen	Capsules	25 mg, 50 mg and 75 mg	Orudis	
Ketorolac Tromethamine	Injection	15 mg/mL and 30 mg/mL	Toradol	
Ketorolac Tromethamine	Ophthalmic Solution	0.5%	Acular	
Ketorolac Tromethamine	Ophthalmic Solution	0.4%	Acular LS	1/28/2005
Ketorolac Tromethamine	Tablets	10 mg	Toradol	
Ketotifen Fumarate	Ophthalmic Solution	0.025%	Zaditor	12/23/2004
Lactulose	Oral Syrup	10 g/15 mL	Cephulac	
Lamivudine and Zidovudine	Tablets	150 mg/300 mg	Combivir	6/26/2007
Lactulose	Oral Syrup	10 g/15 mL	Chronulac	
Lamotrigine	Tablets	25 mg, 100 mg, 150 mg and 200 mg	Lamictal	
Lamotrigine	Chewable Tablets	2 mg, 5 mg and 25 mg	Lamictal CD	
Latanoprost	Ophthalmic Solution	0.005%	Xalatan	
Lansoprazole	Delayed-release Pellets/Capsules	15 mg and 30 mg	Prevacid	12/05/2005
Lansoprazole	Delayed-release Orally Disintegrating	15 mg and 30 mg	Prevacid	12/27/2006

	Tablets			
Letrozole	Tablets	2.5 mg	Femara	3/2/2006
Leuprolide Acetate	Injection (depot)	7.5 mg/vial	Lupron Depot	
Levalbuterol Hydrochloride	Inhalation Solution	0.0103%, 0.021% and 0.042%	Xopenex	6/20/2005
Levalbuterol Hydrochloride	Inhalation Solution	0.25%	Xopenex	5/23/2006
Levetiracetam	Tablets	250 mg, 500 mg and 750 mg	Keppra	
Levetiracetam	Tablets	1000 mg	Keppra	1/24/2007
Levofloxacin	Injection	5 mg/mL; 50 mL, 100 mL and 150 mL vials	Levaquin in Dextrose 5% in Plastic Container	
Levofloxacin	Injection	25 mg/mL	Levaquin	
Levofloxacin	Ophthalmic Solution	0.5%	Quixin	
Levofloxacin	Tablets	250 mg, 500 mg and 750 mg	Levaquin	
Levonorgestrel and Ethinyl Estradiol	Tablets	0.15 mg/0.03 mg	Seasonale	3/29/2004
Levothyroxine Sodium	Tablets	0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.2 mg and 0.3 mg	Levoxyl	
Linezolid	Tablets	600 mg	Zyvox	12/21/2005
Loperamide Hydrochloride and Simethicone	Chewable Tablets	2 mg/125 mg	Imodium Advanced	
Loperamide Hydrochloride and Simethicone	Tablets	2 mg/125 mg	Imodium Advanced	12/29/2004
Loratadine	Syrup	1 mg/mL	Claritin	
Loratadine	Tablets	10 mg	Claritin	
Loratadine	Orally Disintegrating Tablets	10 mg	Claritin RediTabs	
Loratadine/ Pseudoephedrine	Extended-release Tablets	5 mg/120 mg	Claritin D-12 hour	
Loratadine/ Pseudoephedrine	Extended-release Tablets	10 mg/240 mg	Claritin D-24 hour	
Losartan Potassium	Tablets	25 mg, 50 mg,	Cozaar	

		and 100 mg		
Losartan Potassium and Hydrochlorothiazide	Tablets	50 mg/12.5 mg and 100 mg/25 mg	Hyzaar	5/24/2004
Losartan Potassium and Hydrochlorothiazide	Tablets	100 mg/12.5 mg	Hyzaar	4/4/2006
Mefloquine Hydrochloride	Tablets	250 mg	Lariam	
Megestrol Acetate	Oral Suspension	40 mg/mL	Megace	
Mesalamine	Delayed-release Tablets	400 mg	Asacol	6/22/2007
Metaxalone	Tablets	400 mg	Skelaxin	
Metaxalone	Tablets	800 mg	Skelaxin	11/4/2004
Metformin Hydrochloride	Extended-release Tablets	500 mg	Glucophage XR	
Metformin Hydrochloride	Extended-release Tablets	750 mg	Glucophage XR	
Methylphenidate Hydrochloride	Extended-release Capsules	10 mg	Ritalin LA	5/21/2007
Methylphenidate Hydrochloride	Extended-release Capsules	10 mg, 20 mg and 30 mg	Metadate CD	5/13/2005
Methylphenidate Hydrochloride	Extended-release Capsules	20 mg, 30 mg and 40 mg	Ritalin LA	8/21/06
Methylphenidate Hydrochloride	Extended-release Capsules	40 mg	Metadate CD	3/15/2007
Methylphenidate Hydrochloride	Extended-release Tablets	18 mg, 27 mg, 36 mg and 54 mg	Concerta	7/19/2005
Metoclopramide Hydrochloride	Injection	5 mg/mL, 2 mL, 10 mL, 20 mL and 30 mL vials	Reglan	
Metoprolol Succinate	Extended-release Tablets	25 mg, 50 mg, 100 mg and 200 mg	Toprol XL	
Metronidazole	Vaginal Gel	0.75%	MetroGel-Vaginal	9/2/2004
Mirtazapine	Tablets	7.5 mg, 15 mg, 30 mg, and 45 mg	Remeron	
Mirtazapine	Orally Disintegrating Tablets	15 mg, 30 mg and 45 mg	Remeron SolTab	
Modafinil	Tablets	100 mg and 200 mg	Provigil	
Moexipril Hydrochloride	Tablets	7.5 mg and 15	Univasc	

		mg		
Moexipril Hydrochloride and Hydrochlorothiazide	Tablets	7.5mg/12.5mg 15 mg/25 mg and 15 mg/12.5 mg	Uniretic	1/15/2004
Mometasone Furoate	Topical Solution (Cream)	0.1%	Elocon	
Mometasone Furoate	Topical Solution (Lotion)	0.1%	Elocon	6/10/2004
Montelukast Sodium	Chewable Tablets	4 mg and 5 mg	Singulair	12/26/2006
Montelukast	Tablets	10 mg	Singulair	2/20/2007
Montelukast	Tablets	10 mg	Singulair	2/20/2007
Morphine Sulfate	Extended-release Capsules	30 mg, 60 mg, 90 mg and 120 mg	Avinza	6/4/2007
Moxifloxacin Hydrochloride	Ophthalmic Solution/Drops	0.5%	Vigamox	12/22/2005
Moxifloxacin Hydrochloride	Tablets	400 mg	Avelox	
Nabumetone	Tablets	500 mg and 750 mg	Relafen	
Naproxen Sodium	Extended-release Tablets	375 mg (base) and 500 mg (base)	Naprelan	
Nateglinide	Tablets	60 mg and 120 mg	Starlix	12/22/2004
Nefazodone Hydrochloride	Tablets	50 mg, 100 mg, 150 mg 200 mg and 250 mg	Serzone	
Niacin	Extended-release Tablets	500 mg, 750 mg and 1000 mg	Niaspan	
Nicardipine Hydrochloride	Injection	2.5 mg/mL, 10 mL Ampoules	Cardene	12/27/2006
Nicotine	Transdermal System	7 mg/day, 14 mg/day and 21 mg/day	Habitrol	
Nicotine Polacrilex	Troche/Lozenge	2 mg and 4 mg	Commit	
Nifedipine	Capsules	10 mg and 20 mg	Procardia	
Nifedipine	Extended-release Tablets	30 mg, 60 mg and 90 mg	Adalat CC	
Nisoldipine	Extended-release Tablets	40 mg	Sular	6/11/2007
Nifedipine	Extended-release Tablets	30 mg, 60 mg and 90 mg	Procardia XL	

Nitrofurantoin Monohydrate/ Macrocrystals	Capsules	75 mg/25 mg	Macrobid	
Nitroglycerin	Sublingual Tablets	0.3 mg, 0.4 mg and 0.6 mg	Nitrostat	10/19/2005
Nitroglycerin	Transdermal System	0.1 mg/hr	Transderm-Nitro	
Nitroglycerin	Transdermal System	0.1 mg/hr, 0.2 mg/hr, 0.3 mg/hr, 0.4 mg/hr, 0.6 mg/hr and 0.8 mg/hr	Nitro-dur	
Nizatidine	Capsules	150 mg and 300 mg	Axid	
Norelgestromin and Ethinyl Estradiol	Transdermal System	0.15 mg/0.02 mg per 24 hours	Ortho Evra	3/22/2007
Norethindrone/ Ethinyl Estradiol	Tablets	0.5 mg/ 0.035 mg, 0.75 mg/ 0.035 mg and 1 mg /0.035 mg	Ortho-Novum 7/7/7, 21 and 28 day	
Norethindrone Acetate/ Ethinyl Estradiol	Tablets	1 mg/0.005 mg	Femhrt	
Norethindrone Acetate/ Ethinyl Estradiol	Tablets	1 mg/ 0.02 mg, 1 mg/0.03 mg and 1 mg /0.035 mg	Estrostep Fe	
Norethindrone Acetate/ Ethinyl Estradiol	Tablets	1 mg/0.02 mg, 1 mg/ 0.03 mg and 1 mg /0.035 mg	Estrostep 21	
Norethindrone Acetate/ Ethinyl Estradiol and Ferrous Fumarate	Tablets	1 mg/0.02 mg and 75 mg	Loestrin 24 Fe	4/17/2006
Norethindrone and Ethinyl Estradiol and Ferrous Fumarate	Chewable Tablets	0.4 mg/0.035 mg	Ovcon-35 Fe	4/27/2007
Norgestimate/ Ethinyl Estradiol	Tablets	0.18 mg /0.025 mg, 0.215 mg /0.025 mg and 0.25 mg /0.025 mg	Ortho Tri-Cyclen Lo, 28 day	
Norgestimate/ Ethinyl Estradiol	Tablets	0.18 mg /0.035 mg, 0.215 mg /0.035 mg and 0.25 mg /0.035 mg	Ortho Tri-Cyclen, 21 and 28 day	
Nortriptyline Hydrochloride	Capsules	10 mg, 25 mg, 50 mg and 75	Pamelor	

		mg		
Octreotide Acetate	Injection	0.05 mg /mL, 0.1 mg /mL and 0.5 mg/mL, 1 mL vials	Sandostatin (Preservative-free)	
Octreotide Acetate	Injection	0.2 mg/mL and 1 mg /mL, 5 mL vials	Sandostatin	
Ofloxacin	Otic Solution	0.3%	Floxin	
Olanzapine	Tablets	2.5 mg, 5 mg, 7.5 mg, 10 mg and 15 mg	Zyprexa	
Olanzapine	Tablets	20 mg	Zyprexa	
Olanzapine	Orally Disintegrating Tablets	5 mg, 10 mg, 15 mg and 20 mg	Zyprexa Zydis	
Olanzapine and Fluoxetine Hydrochloride	Capsules	6 mg/25 mg, 12 mg/25 mg, 6 mg/50 mg and 12 mg/50 mg	Symbyax	1/10/2005
Olmesartan Medoxomil and Hydrochlorothiazide	Tablets	20 mg/12.5 mg	Benicar HCT	5/11/2007
Omeprazole Magnesium	Delayed-release Capsules	20 mg	Prilosec OTC	3/19/2007
Olmesartan Medoxomil	Tablets	5 mg, 20 mg and 40 mg	Benicar	4/25/2006
Olmesartan Medoxomil and Hydrochlorothiazide	Tablets	40 mg/12.5 mg and 40 mg/25 mg	Benicar HCT	2/15/2007
Olopatadine Hydrochloride	Ophthalmic Solution	0.1%	Patanol	7/17/2006
Omeprazole	Delayed-release Capsules	10 mg, 20 mg and 40 mg	Prilosec	
Omeprazole and Sodium Bicarbonate	Capsules	20 mg/1100 mg and 40 mg/1100 mg	Zegerid	4/30/2007
Ondansetron Hydrochloride	Injection	2 mg/mL, 2 mL vials (Preservative-free)	Zofran	
Ondansetron Hydrochloride	Injection	2 mg/mL, 20 mL vials	Zofran	
Ondansetron Hydrochloride	Injection	0.64 mg/mL, 50 mL container (plastic)	Zofran in Plastic Container	
Ondansetron Hydrochloride	Oral Solution	4 mg/5 mL	Zofran	12/20/2004

Ondansetron Hydrochloride	Orally Disintegrating Tablets	4 mg and 8 mg	Zofran ODT	
Ondansetron Hydrochloride	Tablets	4 mg, 8 mg, 16 mg and 24 mg	Zofran	
Oxaliplatin	For Injection	50 mg/vial and 100 mg/vial	Eloxatin	2/9/2007
Oxaliplatin	Injection	5 mg/mL, 10 mL and 20 mL vials	Eloxatin	2/9/2007
Oxandrolone	Tablets	2.5 mg and 10 mg	Oxandrin	6/19/2006
Oxazepam	Capsules	10 mg, 15 mg and 30 mg	Serax	
Oxcarbazepine [1]	Tablets	150 mg, 300 mg and 600 mg	Trileptal	5/5/2006
Oxcarbazepine	Oral Suspension	300 mg/5 mL	Trileptal	12/26/2006
Oxybutynin Chloride	Extended-release Tablets	5 mg, 10 mg and 15 mg	Ditropan XL	
Oxycodone	Extended-release Tablets	10 mg, 20 mg, 40 mg, 80 mg and 160 mg	Oxycontin	
Oxycodone Hydrochloride	Extended-release Tablets	15 mg	Oxycontin	2/15/2007
Oxycodone Hydrochloride	Extended-release Tablets	30 mg and 60 mg	Oxycontin	1/3/2007
Paclitaxel	Injection	6 mg/mL, 5 mL, 16.7 mL, 25 mL, 33.3 mL and 50 mL vials	Taxol	
Pamidronate Disodium	For Injection	30 mg/vial, 60 mg/vial and 90 mg/vial	Aredia	
Pamidronate Disodium	Injection	30 mg/vial, 60 mg/vial and 90 mg/vial	Aredia	
Pantoprazole Sodium	For Injection	40 mg/vial	Prontonix IV	4/7/2005
Pantoprazole Sodium	Delayed-release Tablets	20 mg and 40 mg	Protonix	2/2/2004
Paroxetine Hydrochloride	Capsules	10 mg and 20 mg	Paxil	
Paroxetine Hydrochloride	Oral Suspension	10 mg/5 mL	Paxil	2/10/2005
Paroxetine Hydrochloride	Tablets	10 mg, 20 mg, 30 mg and 40 mg	Paxil	

Paroxetine Hydrochloride	Extended-release Tablets	25 mg	Paxil CR	9/9/2005
Pergolide Mesylate	Tablets	0.05 mg, 0.25 mg and 1 mg	Permax	
Perindopril Erbumine	Tablets	2 mg, 4 mg and 8 mg	Aceon	6/6/2006
Pioglitazone Hydrochloride	Tablets	15 mg, 30 mg and 45 mg	Actos	
Polyethylene Glycol 3350	Powder for Oral Solution	17g/Scoopful	Miralax	
Potassium Chloride	Extended-release Capsules	8 mEq and 10 mEq	Micro K	
Potassium Chloride	Extended-release Tablets	10 mEq and 20 mEq	K-Dur	
Pramipexole Dihydrochloride	Tablets	0.25 mg	Mirapex	5/27/2005
Pramipexole Dihydrochloride	Tablets	0.125 mg, 0.5 mg, 1 mg and 1.5 mg	Mirapex	6/24/2005
Pravastatin Sodium	Tablets	10 mg, 20 mg, 40 mg and 80 mg	Pravachol	
Pravastatin Sodium	Tablets	30 mg	Pravachol	6/1/2005
Prazosin Hydrochloride	Capsules	1 mg, 2 mg and 5 mg	Minipress	
Prednisolone Sodium Phosphate	Oral Solution	5 mg(base)/ 5 mL and 15 mg (base)/ 5 mL	Pediapred	
Propafenone	Extended-release Capsules	325 mg	Rythmol SR	11/07/2006
Propafenone Hydrochloride	Extended-release Capsules	225 mg and 425 mg	Rythmol SR	10/11/2006
Propofol	Injection	10 mg/mL ; 20 mL, 50 mL and 100 mL vials and 20 mL syringe	Diprivan	
Propranolol Hydrochloride	Extended-release Capsules	60 mg, 80 mg, 120 mg and 160 mg	Inderal LA	
Quetiapine Fumarate	Tablets	25 mg	Seroquel	8/12/2005
Quetiapine Fumarate	Tablets	50 mg, 150 mg and 400 mg	Seroquel	2/12/2007
Quetiapine Fumarate	Tablets	100 mg, 200 mg and 300 mg	Seroquel	2/21/2006
Quinapril Hydrochloride	Tablets	5 mg, 10 mg, 20 mg and 40	Accupril	

		mg		
Quinapril Hydrochloride/ Hydrochlorothiazide	Tablets	10 mg/12.5 mg, 20 mg/12.5 mg and 20mg/25 mg	Accuretic	
Rabeprazole Sodium	Delayed-release Tablets	20 mg	Aciphex	
Raloxifene Hydrochloride	Tablets	60 mg	Evista	
Ramipril	Capsules	1.25 mg, 2.5 mg, 5 mg and 10 mg	Altace	
Ranitidine	Capsules	150 mg and 300 mg	Zantac	
Ranitidine	Injection	25 mg/mL, 2 mL and 6 mL and 40 mL vials	Zantac	
Ranitidine	Oral Solution	15 mg/mL	Zantac	
Ranitidine	Tablets	75 mg, 150 mg and 300 mg	Zantac	
Repaglinide	Tablets	0.5 mg, 1 mg and 2 mg	Prandin	2/10/2005
Ribavirin	Capsules	200 mg	Rebetol	
Risedronate Sodium	Tablets	5 mg, 30 mg and 35 mg	Actonel	4/23/2004
Risperidone	Oral Solution	1 mg/mL	Risperdal	
Risperidone	Tablets	0.25 mg, 1 mg, 2 mg, 3 mg and 4 mg	Risperdal	
Risperidone [1]	Orally Disintegrating Tablets	0.25 mg	Risperdal	4/11/2005
Risperidone	Orally Disintegrating Tablets	0.5 mg, 1 mg and 2 mg	Risperdal	
Risperidone [1]	Orally Disintegrating Tablets	3 mg and 4 mg	Risperdal	3/23/2005
Rivastigmine Tartrate	Capsules	1.5 mg, 3 mg, 4.5 mg and 6 mg	Exelon	4/21/2004
Rivastigmine Tartrate	Oral Solution	2 mg/mL	Exelon	11/5/2004
Rizatriptan Benzoate	Tablets	5 mg and 10 mg	Maxalt	9/2/2004
Rizatriptan Benzoate	Orally Disintegrating Tablets	5 mg and 10 mg	Maxalt-MLT	2/17/2006
Rofecoxib	Tablets	12.5 mg, 25	Vioxx	

		mg and 50 mg		
Ropinirole Hydrochloride	Tablets	0.25 mg, 0.5 mg, 1 mg and 2 mg	Requip	12/22/2004
Ropinirole Hydrochloride	Tablets	3 mg, 4 mg and 5 mg	Requip	2/4/2005
Ropivacaine Hydrochloride	Injection	2 mg/mL, 5 mg/mL and 10 mg/mL, 20 mL, 30 mL and 20 mL vials	Naropin	11/13/2006
Rosiglitazone Maleate	Tablets	2 mg, 4 mg and 8 mg	Avandia	
Rosiglitazone Maleate and Metformin Hydrochloride	Tablets	1 mg/ 500 mg, 2 mg/ 500mg, 4 mg/ 500 mg, 2 mg/ 1000 mg and 4 mg/ 1000 mg	Avandamet	10/22/2004
Rosuvastatin Calcium	Tablets	5 mg, 10 mg, 20 mg and 40 mg	Crestor	8/13/2007
Sertraline Hydrochloride	Oral Concentrate	20 mg/mL	Zoloft	
Sertraline Hydrochloride	Tablets	25 mg, 50 mg and 100 mg	Zoloft	
Sertraline Hydrochloride	Tablets	150 mg and 200 mg	Zoloft	11/9/2005
Sevoflurane	Inhalation	100%, 250 mL	Ultane	
Sildenafil Citrate	Tablets	25 mg and 50 mg	Viagra	11/19/2004
Sildenafil Citrate	Tablets	100 mg	Viagra	10/25/2004
Silver Sulfadiazine	Cream	1%	Silvadene	
Simvastatin	Tablets	5 mg, 10 mg, 20 mg, 40 mg and 80 mg	Zocor	
Sumatriptan Succinate	Injection	6 mg/0.5 mL, 0.5 mL vials	Imitrex	10/25/2004
Sumatriptan Succinate	Injection	6 mg/0.5 mL, 0.5 mL (prefilled syringes)	Imitrex	5/9/2006
Sumatriptan Succinate	Tablets	25 mg, 50 mg and 100 mg	Imitrex	
Tamoxifen Citrate	Tablets	10 mg and 20 mg	Nolvadex	
Tamsulosin Hydrochloride	Capsules	0.4 mg	Flomax	12/20/2004
Telmisartan	Tablets	20 mg, 40 mg	Micardis	12/26/2006

		and 80 mg		
Temazepam	Capsules	7.5 mg	Restoril	11/01/2006
Temozolomide	Capsules	5 mg, 20 mg, 100 mg, and 250 mg	Temodar	3/20/2007
Terazosin Hydrochloride	Capsules	1 mg, 2 mg, 5 mg and 10 mg	Hytrin	
Terazosin Hydrochloride	Tablets	1 mg, 2 mg, 5 mg and 10 mg	Hytrin	
Terbinafine Hydrochloride	Tablets	250 mg	Lamisil	
Terfenadine	Tablets	60 mg	Seldane	
Testosterone	Gel	1%	Androgel	
Thalidomide	Capsules	50 mg and 100 mg	Thalomid	12/18/2006
Thalidomide	Capsules	200 mg	Thalomid	9/25/2006
Tiagabine Hydrochloride	Tablets	2 mg and 4 mg	Gabitril	2/1/2005
Ticlopidine Hydrochloride	Tablets	250 mg	Ticlid	
Timolol Maleate	Ophthalmic Solution	0.25% and 0.5%	Timoptic	
Tizanidine Hydrochloride	Capsules	2 mg, 4 mg and 6 mg	Zanaflex	8/10/2007
Tolterodine Tartrate	Extended-release Capsules	2 mg and 4 mg	Detrol LA	7/30/2007
Tolterodine Tartrate	Tablets	1 mg and 2 mg	Detrol	
Topiramate	Capsules	15 mg and 25 mg	Topamax Sprinkle	9/7/2005
Topiramate	Tablets	25 mg, 100 mg and 200 mg	Topamax	12/26/2001
Topiramate	Tablets	50 mg	Topamax	9/8/2005
Torsemide	Tablets	5 mg, 10 mg, 20 mg, and 100 mg	Demadex	
Tramadol Hydrochloride	Tablets	50 mg	Ultram	
Tramadol Hydrochloride	Extended-release Tablets	100 mg	Ultram ER	1/8/2007
Tramadol Hydrochloride	Extended-release Tablets	200 mg	Ultram ER	3/28/2007
Tramadol Hydrochloride	Extended-release Tablets	300 mg	Ultram ER	9/25/2007
Trandolapril	Tablets	1 mg, 2 mg and 4 mg	Mavik	10/4/2004
Trandolapril/Verapamil Hydrochloride	Extended-release Tablets	4 mg/ 240 mg	Tarka	7/24/2007
Trazodone Hydrochloride	Tablets	150 mg	Desyrel	
Tretinoin	Cream	0.025%, 0.05% and	Retin-A	

		0.1%		
Tretinoin	Gel	0.025%	Retin-A	
Triamcinolone Acetonide	Nasal Spray	0.055 mg/Spray	Nasacort AQ	12/29/2005
Triamterene/ Hydrochlorothiazide	Tablets	37.5 mg/25 mg and 75 mg/50 mg	Maxzide	
Valacyclovir Hydrochloride	Tablets	500 mg and 1 g	Valtrex	
Valganciclovir Hydrochloride	Tablets	450 mg	Valcyte	12/27/2005
Valsartan	Tablets	40 mg, 80 mg, 160 mg and 320 mg	Diovan	12/28/2004
Valsartan and Hydrochlorothiazide	Tablets	80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg	Diovan HCT	12/2/2005
Valsartan and Hydrochlorothiazide	Tablets	320 mg/12.5 mg and 320 mg/25 mg	Diovan HCT	2/7/2007
Venlafaxine Hydrochloride	Extended-release Capsules	37.5 mg, 75 mg and 150 mg	Effexor XR	
Venlafaxine Hydrochloride	Tablets	25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg	Effexor	11/03/2005
Venlafaxine Hydrochloride	Extended-release Tablets	37.5 mg, 75 mg and 150 mg	Effexor XR	5/3/2007
Vecuronium Bromide	For Injection	10 mg/vial and 20 mg/vial	Norcuron	
Verapamil Hydrochloride	Extended-release Capsules	100 mg and 200 mg	Verelan PM	7/20/2006
Verapamil Hydrochloride	Extended-release Capsules	120 mg, 180 mg and 240 mg	Verelan SR	
Verapamil Hydrochloride	Extended-release Tablets	180 mg	Isoptin SR	
Verapamil Hydrochloride	Extended-release Tablets	240 mg	Covera HS	
Verapamil Hydrochloride	Extended-release Capsules	300 mg	Verelan PM	5/19/2006
Vincristine Sulfate	Injection	1 mg/mL, 1 mL, 2 mL and 5 mL vials	Oncovin	

Zaleplon	Capsules	5 mg and 10 mg	Sonata	6/21/2005
Zidovudine	Capsules	100 mg	Retrovir	
Ziprasidone Hydrochloride	Capsules	20 mg, 40 mg, 60 mg and 80 mg	Geodon	2/7/2005
Zolpidem Tartrate	Extended-release Tablets	6.25 mg	Ambien CR	2/24/2006
Zolpidem Tartrate	Extended-release Tablets	12.5 mg	Ambien CR	1/19/2006

* ANDA withdrawn

Footnote:
[1] Date of Submission has been updated.

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Date created: February 16, 2005; Last updated: November 16, 2007

EXHIBIT 11

H.R. REP. 98-857(I), H.R. Rep. No. 857(I), 98TH Cong., 2ND Sess. 1984, 1984 U.S.C.C.A.N. 2647, 1984 WL 37416 (Leg.Hist.)

(Cite as: H.R. REP. 98-857(I), 1984 U.S.C.C.A.N. 2647)

****2647** P.L. 98-417, DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT
SEE PAGE 98 STAT. 1585
SENATE REPORT (JUDICIARY COMMITTEE) NO. 98-547, JUNE 26, 1984 (TO ACCOMPANY S. 1538)
HOUSE REPORT (ENERGY AND COMMERCE COMMITTEE) NO. 98-857(I), JUNE 21, 1984 (TO ACCOMPANY H.R. 3605)
HOUSE REPORT (JUDICIARY COMMITTEE) NO. 98-857(II), AUG. 1, 1984 (TO ACCOMPANY H.R. 3605)
CONG. RECORD VOL. 130 (1984)
DATES OF CONSIDERATION AND PASSAGE
SENATE JUNE 29, AUGUST 10, SEPTEMBER 12, 1984
HOUSE SEPTEMBER 6, 1984
S. 1538 WAS PASSED IN LIEU OF THE HOUSE BILL AFTER AMENDING ITS LANGUAGE TO CONTAIN THE TEXT OF THE HOUSE BILL. THE HOUSE REPORT (PART I, THIS PAGE, AND PART II, PAGE 2686) AND A RELATED REPORT (PAGE 2721) ARE SET OUT.

(CONSULT NOTE FOLLOWING TEXT FOR INFORMATION ABOUT OMITTED MATERIAL. EACH COMMITTEE REPORT IS A SEPARATE DOCUMENT ON WESTLAW.)

HOUSE REPORT NO. 98-857(I)
JUNE 21, 1984

***1** THE COMMITTEE ON ENERGY AND COMMERCE, TO WHOM WAS REFERRED THE BILL (H.R. 3605) TO AMEND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO AUTHORIZE AN ABBREVIATED NEW DRUG APPLICATION UNDER SECTION 505 OF THAT ACT FOR GENERIC NEW DRUGS EQUIVALENT TO APPROVED NEW DRUGS, HAVING CONSIDERED THE SAME, REPORT FAVORABLY THEREON WITH AMENDMENTS AND RECOMMEND THAT THE BILL AS AMENDED DO PASS.

* * * *

***14** PURPOSE AND SUMMARY

TITLE I

THE PURPOSE OF TITLE I OF THE BILL IS TO MAKE AVAILABLE MORE LOW COST GENERIC DRUGS BY ESTABLISHING A GENERIC DRUG APPROVAL PROCEDURE FOR PIONEER DRUGS FIRST APPROVED AFTER 1962. UNDER CURRENT LAW, THERE IS A GENERIC DRUG APPROVAL PROCEDURE FOR PIONEER DRUGS APPROVED BEFORE 1962, BUT NOT FOR PIONEER DRUGS APPROVED AFTER 1962.

TITLE I OF THE BILL GENERALLY EXTENDS THE PROCEDURES USED TO APPROVE GENERIC

H.R. REP. 98-857(I), H.R. Rep. No. 857(I), 98TH Cong., 2ND Sess. 1984, 1984 U.S.C.C.A.N. 2647, 1984 WL 37416 (Leg.Hist.)

(Cite as: H.R. REP. 98-857(I), 1984 U.S.C.C.A.N. 2647)

COPIES OF PRE-62 DRUGS TO POST-62 DRUGS. GENERIC COPIES ***15 ****2648** OF ANY DRUGS MAY BE APPROVED IF THE GENERIC IS THE SAME AS THE ORIGINAL DRUG OR SO SIMILAR THAT FDA HAS DETERMINED THE DIFFERENCES DO NOT REQUIRE SAFETY AND EFFECTIVENESS TESTING.

TITLE I ALSO REQUIRES PATENT OWNERS TO SUBMIT INFORMATION TO FDA REGARDING PRODUCE AND USE PATENTS THAT COVER APPROVED DRUGS. GENERIC COPIES OF THESE DRUGS MAY BE APPROVED WHEN THE PATENTS EXPIRE UNLESS THE GENERIC COMPANY CERTIFIES THAT THE PATENT IS INVALID OR WILL NOT BE INFRINGED. IN SUCH CASES, THE GENERIC COMPANY MUST NOTIFY THE PATENT OWNER ABOUT ITS CERTIFICATION AND APPROVAL OF THE GENERIC DRUG MAY NOT BE MADE EFFECTIVE UNTIL THE COURT DECIDES THE SUIT FOR PATENT INFRINGEMENT OR A PERIOD OF 18 MONTHS, WHICHEVER OCCURS FIRST. NOTIFICATION MUST BE GIVEN WHEN THE GENERIC HAS SUBMITTED AN ANDA WITH BIOEQUIVALENCE DATA.

IN ADDITION, TITLE I AFFORDS FOUR YEARS OF EXCLUSIVE MARKET LIFE TO DRUGS WHICH MAY NOT BE PATENTED AND WHICH ARE APPROVED FOR THE FIRST TIME AFTER ENACTMENT OF THE BILL. FURTHER, DRUGS WHICH WERE APPROVED FOR THE FIRST TIME BETWEEN 1982 AND THE DATE OF ENACTMENT RECEIVED TEN YEARS OF EXCLUSIVE MARKET LIFE.

TITLE II

THE PURPOSE OF TITLE II OF THE BILL IS TO CREATE A NEW INCENTIVE FOR INCREASED EXPENDITURES FOR RESEARCH AND DEVELOPMENT OF CERTAIN PRODUCTS WHICH ARE SUBJECT TO PREMARKET GOVERNMENT APPROVAL. THE INCENTIVE IS THE RESTORATION OF SOME OF THE TIME LOST ON PATENT LIFE WHILE THE PRODUCT IS AWAITING PRE-MARKET APPROVAL. UNDER CURRENT LAW, A PATENT CONTINUES TO RUN WHILE THE MAKER OF THE PRODUCT IS TESTING AND AWAITING APPROVAL TO MARKET IT.

TITLE II OF H.R. 3605 PROVIDES FOR ONE EXTENSION OF THE EARLIEST PATENT ON CERTAIN PRODUCTS SUBJECT TO PRE-MARKET APPROVAL. THE EXTENSION WOULD BE FOR A PERIOD EQUAL TO: (1) HALF OF THE TIME REQUIRED TO TEST THE PRODUCT FOR SAFETY (AND EFFECTIVENESS IN SOME CASES); AND (2) ALL OF THE TIME REQUIRED FOR THE AGENCY TO APPROVE MARKETING OF THE PRODUCT. THESE PRODUCTS INCLUDE: HUMAN DRUGS, ANIMAL DRUGS, MEDICAL DEVICES, AND FOOD AND COLOR ADDITIVES.

TITLE II PLACES SEVERAL LIMITS ON THE PERIOD OF PATENT EXTENSION. FIRST, THE PERIOD OF EXTENSION MAY NOT EXCEED TWO YEARS FOR PRODUCTS EITHER CURRENTLY BEING TESTED OR AWAITING APPROVAL. FOR ALL OTHER PRODUCTS, THE PERIOD OF EXTENSION MAY NOT EXCEED FIVE YEARS. SECOND, THE PERIOD OF PATENT EXTENSION WHEN ADDED TO THE PATENT TIME LEFT AFTER APPROVAL OF THE PRODUCT MAY NOT EXCEED FOURTEEN YEARS. THIRD, ANY TIME THAT THE PRODUCT'S MANUFACTURER DID NOT ACT WITH DUE DILIGENCE DURING THE REGULATORY REVIEW PERIOD WOULD BE SUBTRACTED.

FINALLY, TITLE II PROVIDES THAT IT IS NOT AN ACT OF PATENT INFRINGEMENT FOR A GENERIC DRUG MAKER TO IMPORT OR TO TEST A PATENTED DRUG IN PREPARATION FOR SEEKING FDA APPROVAL IF MARKETING OF THE DRUG WOULD OCCUR AFTER EXPIRATION OF THE PATENT.

HEARINGS

THE COMMITTEE'S SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT HELD ONE DAY OF HEARINGS ON H.R. 3605, THE DRUG PRICE COMPETITION ACT, ON JULY 15, 1983. TESTIMONY WAS RECEIVED FROM 15 WITNESSES, ***16 ****2649** REPRESENTING NINE ORGANIZATIONS, WITH

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ADDITIONAL MATERIAL SUBMITTED BY TWO INDIVIDUALS AND ORGANIZATIONS.

COMMITTEE CONSIDERATION

ON AUGUST 2, 1983, THE COMMITTEE'S SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT MET IN OPEN SESSION AND ORDERED FAVORABLY REPORTED H.R. 3605 WITHOUT AMENDMENT BY VOICE VOTE. ON JUNE 12, 1984, THE COMMITTEE MET IN OPEN SESSION ON H.R. 3605, AMENDED THE BILL, AND ORDERED IT FAVORABLY REPORTED BY A VOICE VOTE. THE TITLE OF THE BILL, AS AMENDED, IS THE 'DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984.'

BACKGROUND AND NEED FOR THE LEGISLATION

TITLE I-- ABBREVIATED NEW DRUG APPLICATIONS

PRIOR TO 1962, THE FEDERAL FOOD, DRUG AND COSMETIC ACT (FFDCA) REQUIRED THAT ALL DRUGS BE APPROVED AS SAFE BEFORE THEY COULD BE MARKETED. THE 1962 AMENDMENTS REQUIRED THAT ALL NEW DRUGS, GENERIC AND PIONEER, MUST BE APPROVED AS SAFE AND EFFECTIVE PRIOR TO MARKETING.

AS A RESULT OF THE 1962 AMENDMENTS, FDA DID TWO THINGS REGARDING PRE-1962 DRUGS. FIRST, THE AGENCY CREATED THE DRUG EFFICACY STUDY (DESI) TO DETERMINE IF ALL PRE-1962 DRUGS WERE EFFECTIVE. SECOND, FDA ESTABLISHED A POLICY PERMITTING THE APPROVAL OF A GENERIC DRUG EQUIVALENT TO A SAFE AND EFFECTIVE PRE-1962 PIONEER DRUG.

AS A RESULT OF THE 1962 AMENDMENTS, THE MANUFACTURER OF A PIONEER DRUG MUST CONDUCT TESTS ON HUMANS THAT SHOW THE PRODUCT TO BE SAFE AND EFFECTIVE AND SUBMIT THE RESULTS IN A NEW DRUG APPLICATION (NDA). A MANUFACTURER OF A GENERIC DRUG MUST CONDUCT TESTS THAT SHOW THE GENERIC DRUG IS THE SAME AS THE PIONEER DRUG AND THAT IT WILL BE PROPERLY MANUFACTURED AND LABELED. THIS INFORMATION IS SUBMITTED IN AN ABBREVIATED NEW DRUG APPLICATION (ANDA).

THE ONLY DIFFERENCE BETWEEN A NDA AND AN ANDA IS THAT THE GENERIC MANUFACTURER IS NOT REQUIRED TO CONDUCT HUMAN CLINICAL TRIALS. FDA CONSIDERS SUCH RETESTING TO BE UNNECESSARY AND WASTEFUL BECAUSE THE DRUG HAS ALREADY BEEN DETERMINED TO BE SAFE AND EFFECTIVE. MOREOVER, SUCH RETESTING IS UNETHICAL BECAUSE IT REQUIRES THAT SOME SICK PATIENTS TAKE PLACEBOS AND BE DENIED TREATMENT KNOWN TO BE EFFECTIVE.

THE FDA ALLOWS THIS ANDA PROCEDURE ONLY FOR PIONEER DRUGS APPROVED BEFORE 1962. THERE IS NO ANDA PROCEDURE FOR APPROVING GENERIC EQUIVALENTS OF PIONEER DRUGS APPROVED AFTER 1962. WHILE THE FDA HAS BEEN CONSIDERING SINCE 1978 AN EXTENSION OF THE PRE-1962 ANDA POLICY TO POST-1962 DRUGS, IT HAS NOT EXTENDED THE REGULATION. BECAUSE OF THE AGENCY'S FAILURE TO ACT, TITLE I OF H.R. 3605 IS NECESSARY TO ESTABLISH A POST-1962 ANDA POLICY.

SOME HAVE SUGGESTED THAT 'PAPER NDAS' BE USED TO APPROVE GENERIC EQUIVALENTS OF PIONEER DRUGS APPROVED AFTER 1962. UNDER THE PAPER NDA PROCEDURE, THE GENERIC MANUFACTURER MAY SUBMIT SCIENTIFIC REPORTS, INSTEAD OF CLINICAL TRIALS, TO SUPPORT FINDINGS OF SAFETY AND EFFICACY. THIS PROCEDURE IS INADEQUATE, HOWEVER, BECAUSE FDA ESTIMATES THAT SATISFACTORY REPORTS ARE NOT AVAILABLE FOR 85 PERCENT OF ALL

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POST-1962 DRUGS.

***17 **2650** CURRENTLY, THERE ARE APPROXIMATELY 150 DRUGS APPROVED AFTER 1962 THAT ARE OFF PATENT AND FOR WHICH THERE IS NO GENERIC EQUIVALENT. ALL OF THESE DRUGS COULD BE APPROVED IN GENERIC FORM IF THERE WAS A PROCEDURE. EACH YEAR, MORE PIONEER DRUGS GO OFF PATENT AND BECOME AVAILABLE FOR APPROVAL AS GENERICS.

AMONG THE DRUGS AVAILABLE OR SOON TO BE AVAILABLE FOR GENERIC APPROVAL ARE FIVE BEST SELLERS: VALIUM, MOTRIN, INDERAL, DYAZIDE, AND LASIX. DYAZIDE, FOR EXAMPLE, IS THE MOST WIDELY USED DIURETIC FOR THE TREATMENT OF HIGH BLOOD PRESSURE. ITS PATENT EXPIRED IN 1981. VALIUM IS A POPULAR TRANQUILIZER WHOSE PATENT EXPIRES IN 1985. ANOTHER DRUG WHOSE PATENT HAS EXPIRED IS INDOCIN, AN ANTI-INFLAMMATORY DRUG USED IN THE TREATMENT OF ARTHRITIS THAT IS THE TENTH HIGHEST SELLING DRUG IN THE UNITED STATES.

THE AVAILABILITY OF GENERIC VERSIONS OF PIONEER DRUGS APPROVED AFTER 1962 WOULD SAVE AMERICAN CONSUMERS $920 MILLION OVER THE NEXT 12 YEARS. OLDER AMERICANS, IN PARTICULAR, WOULD BENEFIT BECAUSE THEY USE ALMOST 25 PERCENT OF ALL PRESCRIPTION DRUGS.

MOREOVER, THE LACK OF GENERICS FOR POST-1962 PIONEER DRUGS WILL COST FEDERAL AND STATE GOVERNMENTS MILLIONS OF DOLLARS. FOR THE DRUG METRONIDAZOLE, PURCHASED BY THE DEPARTMENT OF DEFENSE, THE TAXPAYERS SAVED APPROXIMATELY $1.2 MILLION IN ONE YEAR AS A RESULT OF THE AVAILABILITY OF A LOWER PRICED GENERIC VERSION. FEDERAL AND STATE GOVERNMENTS WILL BE DENIED COMPARABLE SAVINGS ON DRUGS APPROVED AFTER 1962 BECAUSE OF THE LACK OF AN APPROVAL PROCEDURE.

TITLE II-- PATENT TERM RESTORATION

PATENTS ARE DESIGNED TO PROMOTE INNOVATION BY PROVIDING THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING, OR SELLING AN INVENTION. THEY ENABLE INNOVATORS TO OBTAIN GREATER PROFITS THAN COULD HAVE BEEN OBTAINED IF DIRECT COMPETITION EXISTED. THESE PROFITS ACT AS INCENTIVES FOR INNOVATIVE ACTIVITIES.

ALTHOUGH THE PATENT TERM IN THE UNITED STATES IS 17 YEARS, THE PERIOD DURING THE PATENT TERM IN WHICH PRODUCTS ARE MARKETED (THE EFFECTIVE PATENT TERM) IS USUALLY LESS THAN 17 YEARS BECAUSE PATENTS OFTEN ARE OBTAINED BEFORE PRODUCTS ARE READY TO BE MARKETED.

EFFECTIVE PATENT TERMS ARE INFLUENCED BY MANY FACTORS, INCLUDING FEDERAL PREMARKETING AND PREMANUFACTURING REGULATIONS. THE PRODUCTS COVERED BY THESE REGULATIONS INCLUDE PHARMACEUTICALS, MEDICAL DEVICES, FOOD ADDITIVES, AND COLOR ADDITIVES. PHARMACEUTICALS FOR INSTANCE CANNOT BE MARKETED IN THE UNITED STATES UNTIL THEY HAVE BEEN APPROVED BY THE FOOD AND DRUG ADMINISTRATION (FDA). TO OBTAIN SUCH APPROVAL, DRUGS MUST UNDERGO EXTENSIVE TESTING TO PROVE THEY ARE BOTH SAFE AND EFFECTIVE. ALL THESE PRODUCTS ARE SUBJECT TO DIFFERENT REGULATIONS THAT HAVE HAD VARYING IMPACTS ON EFFECTIVE PATENT TERMS.

IN TESTIMONY BEFORE SEVERAL CONGRESSIONAL COMMITTEES, REPRESENTATIVES FROM THE PHARMACEUTICAL FIRMS THAT ARE HEAVILY INVOLVED IN BASIC RESEARCH AND RELY UPON PATENTS, CLAIMED THAT THE AVERAGE EFFECTIVE PATENT TERM OF DRUGS HAS DECLINED. THEY ARGUED THAT A CONTINUATION OF THE DECLINE WOULD RESULT IN DECREASED EXPENDITURES FOR RESEARCH AND DEVELOPMENT AND, EVENTUALLY, IN A DECLINE IN THE INTRODUCTION OF NEW DRUGS.

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***18 **2651** AS COMPENSATION FOR THE LOSS OF PATENT TERM DUE TO GOVERNMENT REVIEW, THE RESEARCH INTENSIVE FIRMS ARGUED FOR PATENT TERM EXTENSION LEGISLATION. THEY STATED THAT THE LEGISLATION WOULD CREATE A SIGNIFICANT, NEW INCENTIVE WHICH WOULD RESULT IN INCREASED EXPENDITURES FOR RESEARCH AND DEVELOPMENT, AND ULTIMATELY IN MORE INNOVATIVE DRUGS.

COMMITTEE OVERSIGHT FINDINGS

PURSUANT TO CLAUSE 2(1)(3)(A) OF RULE XI OF THE RULES OF THE HOUSE OF REPRESENTATIVES, THE COMMITTEE REPORTS THAT OVERSIGHT OF THE FOOD AND DRUG ADMINISTRATION AND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT WAS CONDUCTED BY THE SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT. A HEARING WAS HELD ON JULY 15, 1983. THE FINDINGS OF THE COMMITTEE'S OVERSIGHT ACTIVITIES HAVE BEEN INCORPORATED INTO THE LEGISLATION AND ARE DISCUSSED IN THOSE PORTIONS OF THIS REPORT ENTITLED 'BACKGROUND AND NEED FOR THE LEGISLATION' AND 'SECTION-BY-SECTION ANALYSIS.'

COMMITTEE ON GOVERNMENT OPERATIONS

PURSUANT TO CLAUSE 2(1)(3)(D) OF RULE XI OF THE RULES OF THE HOUSE OF REPRESENTATIVES, NO OVERSIGHT FINDINGS HAVE BEEN SUBMITTED TO THE COMMITTEE BY THE COMMITTEE ON GOVERNMENT OPERATIONS.

COMMITTEE COST ESTIMATE

IN COMPLIANCE WITH CLAUSE 7(A) OF RULE XIII OF THE RULES OF THE HOUSE OF REPRESENTATIVES, THE COMMITTEE BELIEVES THAT THE COSTS, IF ANY, INCURRED IN CARRYING OUT H.R. 3605 WILL BE OFFSET BY SAVINGS TO THE FEDERAL GOVERNMENT. IN TESTIFYING BEFORE THE COMMITTEE'S SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT, OFFICIALS FROM THE FOOD AND DRUG ADMINISTRATION ESTIMATED THAT ANY GREATER WORKLOAD RESULTING FROM THE APPROVAL OF GENERIC DRUGS UNDER TITLE I WOULD BE ABSORBED INITIALLY. LATER, THE OFFICIALS ESTIMATED, SOME ADDITIONAL STAFF MIGHT BE REQUIRED TO PROCESS GENERIC DRUG APPLICATIONS. THIS ADDITIONAL STAFF COULD COST UP TO $1.1 MILLION. THE ACTUAL COST TO THE FEDERAL GOVERNMENT CANNOT BE ESTIMATED BECAUSE IT IS UNKNOWN HOW MUCH ADDITIONAL STAFF, IF ANY, MIGHT BE HIRED.

ENACTMENT OF THE LEGISLATION, HOWEVER, WILL RESULT IN SIGNIFICANT COST SAVINGS TO THE FEDERAL GOVERNMENT. UNLIKE THE COSTS OF H.R. 3605, THESE SAVINGS ARE CERTAIN. THE FEDERAL GOVERNMENT SPENT ABOUT $2.4 BILLION FOR DRUGS IN 1983. MANY OF THESE DRUGS WILL BE AVAILABLE AS LOW COST GENERIC AFTER ENACTMENT OF H.R. 3605. FOR EXAMPLE, THE DEPARTMENT OF DEFENSE SAVED APPROXIMATELY $1.2 MILLION IN ONE YEAR WHEN A LOWER PRICED GENERIC VERSION OF METRONIDAZOLE BECAME AVAILABLE.

CONGRESSIONAL BUDGET OFFICE ESTIMATE

PURSUANT TO CLAUSES 2(1)(3)(B) AND (C) OF RULE XI OF THE RULES OF THE HOUSE OF REPRESENTATIVES, THE COMMITTEE SETS FORTH THE FOLLOWING LETTER AND COST ESTIMATE PREPARED BY THE CONGRESSIONAL BUDGET OFFICE WITH RESPECT TO THE REPORTED BILL:

***19 **2652** U.S. CONGRESS,

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CONGRESSIONAL BUDGET OFFICE,
WASHINGTON, DC, JUNE 19, 1984
HON. JOHN D. DINGELL,
CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE,
HOUSE OF REPRESENTATIVES, WASHINGTON, DC.

DEAR MR. CHAIRMAN: THE CONGRESSIONAL BUDGET OFFICE HAS REVIEWED H.R. 3605, THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984, AS ORDERED REPORTED BY THE HOUSE COMMITTEE ON ENERGY AND COMMERCE ON JUNE 12, 1984.

TITLE I OF THIS BILL WOULD ALLOW DRUG MANUFACTURERS TO USE AN ABBREVIATED NEW DRUG APPLICATION (ANDA) WHEN SEEKING APPROVAL TO MAKE GENERIC COPIES OF DRUGS THAT WERE APPROVED BY THE FOOD AND DRUG ADMINISTRATION (FDA) AFTER 1962. AN ESTIMATED 150 DRUG PRODUCTS APPROVED AFTER 1962 ARE CURRENTLY OFF PATENT AND WOULD BECOME AVAILABLE FOR GENERIC COPY USING THE ANDA PROCEDURE PROPOSED IN THIS BILL.

THE FDA ESTIMATES THAT THE ENACTMENT OF H.R. 3605 WOULD AT LEAST TRIPLE THE WORKLOAD OF THE DIVISION RESPONSIBLE FOR APPROVING ANDAS. CURRENTLY, THIS DIVISION REVIEWS ANDAS FOR GENERIC COPIES OF PRE-1962 APPROVED DRUG PRODUCTS. THE WORKLOAD WOULD INCREASE AS SEVERAL MANUFACTURERS FILE AN ANDA FOR EACH DRUG PRODUCT THAT BECOMES AVAILABLE FOR GENERIC COPY. BECAUSE THEY WOULD BE REVIEWING INFORMATION ON NEW DRUGS, THE FDA BELIEVES IT WOULD TAKE THEM A YEAR TO PROCESS EACH OF THE NEW APPLICATIONS. THIS IS ABOUT THREE MONTHS LONGER ON AVERAGE THAN IT CURRENTLY TAKES TO PROCESS A PRE-1962 ANDA. DR. MARVIN SEIFE, DIRECTOR OF FDA'S DIVISION OF GENERIC DRUG MONOGRAPHS, TESTIFIED BEFORE THE SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT THAT A GREATER WORKLOAD COULD AT FIRST BE ABSORBED, BUT MAY LATER REQUIRE ADDITIONAL OFFICE SPACE AND 15 NEW FDA EMPLOYEES. ASSUMING AN AVERAGE FULL-TIME EQUIVALENT POSITION PLUS OVERHEAD AND FRINGE BENEFITS IS $70,000, THE POTENTIAL COST TO THE FDA OF IMPLEMENTING THIS LEGISLATION COULD BE ABOUT $1.1 MILLION. THE ACTUAL COST TO THE FEDERAL GOVERNMENT WOULD DEPEND ON THE EXTENT TO WHICH THE FDA WOULD EXPAND TO ACCOMMODATE THE INCREASED WORKLOAD.

ENACTMENT OF THIS LEGISLATION COULD ALSO RESULT IN SAVINGS TO BOTH THE FEDERAL AND STATE AND LOCAL GOVERNMENTS. IN FISCAL YEAR 1983, THE FEDERAL GOVERNMENT SPENT APPROXIMATELY $2.4 BILLION FOR DRUGS IN THE MEDICAID PROGRAM, AND IN VETERAN AND MILITARY HOSPITALS. DATA ON DRUG COSTS IN THE MEDICARE PROGRAM ARE UNAVAILABLE. IF THE FEDERAL GOVERNMENT IS CURRENTLY PURCHASING THESE 150 COPIABLE DRUG PRODUCTS AT HIGHER, BRAND NAME PRICES, SAVINGS MAY RESULT IF LOWER PRICED, GENERIC COPIES OF THESE DRUGS ARE SUBSTITUTED.

IT IS DIFFICULT TO KNOW IN ADVANCE WHICH OF THE AVAILABLE 150 DRUG PRODUCTS MANUFACTURERS WOULD CHOOSE TO COPY. IT IS ALSO DIFFICULT TO ESTIMATE THE PRICE AT WHICH THESE GENERIC COPIES WOULD BE SOLD. GENERIC VERSIONS OF TEN POPULAR DRUG PRODUCTS SHOW THEIR PRICE TO BE ON AVERAGE 50 PERCENT LESS THAN THEIR BRAND NAME EQUIVALENT. THE DOLLAR AMOUNT OF THE FEDERAL GOVERNMENT CURRENTLY SPENT ON THESE 150 BRAND NAME DRUG PRODUCTS IS UNKNOWN.

TITLE II OF THIS BILL WOULD EXTEND THE AMOUNT OF TIME FOR WHICH CERTAIN PATENTS ARE ISSUED TO INCLUDE SOME OR ALL OF THE TIME REQUIRED**2653 *20 FOR A MANUFACTURER TO TEST A PRODUCT FOR SAFETY AND EFFICACY AND TO RECEIVE MARKETING APPROVAL. PRODUCTS AFFECTED BY THIS LEGISLATION WOULD BE DRUGS, MEDICAL DEVICES, AND FOOD AND COLOR ADDITIVES. MANUFACTURERS MUST SHOW DUE DILIGENCE IN THEIR PRODUCT TESTING OR THIS AMOUNT OF TIME WILL BE SUBTRACTED FROM THE TOTAL LIFE OF

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THE PATENT. THIS PROVISION WOULD PLACE AN ADDITIONAL BURDEN ON THE FDA. THEY WOULD BE RESPONSIBLE FOR KEEPING TRACK OF A MANUFACTURER'S PRODUCT TESTING TIME AND FOR DETERMINING THEIR DILIGENCE IN COMPLETING THE TESTING. THESE COSTS, HOWEVER, WOULD BE NEGLIGIBLE.

ENACTMENT OF THIS BILL COULD RESULT IN INCREASED PERSONNEL COSTS TO THE FEDERAL GOVERNMENT OF APPROXIMATELY $1.1 MILLION. THE BILL, HOWEVER, DOES NOT SPECIFICALLY AUTHORIZE ADDITIONAL APPROPRIATIONS FOR THE FDA. THIS BILL MAY ALSO RESULT IN SAVINGS IF CHEAPER, GENERIC DRUGS ARE MADE AVAILABLE FOR PURCHASE BY THE FEDERAL GOVERNMENT. THESE SAVINGS WOULD OCCUR IN VARIOUS PROGRAMS THROUGHOUT THE BUDGET SUCH AS MEDICARE, MEDICAID, AND THE VETERANS ADMINISTRATION. HOWEVER, THE MAGNITUDE OF THESE SAVINGS IS UNKNOWN.

PLEASE CALL ME IF I CAN BE OF ADDITIONAL ASSISTANCE, OR YOUR STAFF MAY WISH TO CONTACT CARMELA PENA (226-2820) OF OUR BUDGET ANALYSIS DIVISION FOR FURTHER DETAILS ON THIS ESTIMATE.

SINCERELY,

ERIC HANUSHEK

(FOR RUDOLPH G. PENNER, DIRECTOR).

INFLATIONARY IMPACT STATEMENT

PURSUANT TO CLAUSE 2(1)(4) OF RULE XI OF THE RULES OF THE HOUSE OF REPRESENTATIVES, THE COMMITTEE MAKES THE FOLLOWING STATEMENT WITH REGARD TO THE INFLATIONARY IMPACT OF THE REPORTED BILL:

THE COMMITTEE BELIEVES THAT ENACTMENT OF H.R. 3605 WILL NOT HAVE AN INFLATIONARY IMPACT UPON THE ECONOMY. IN FACT, TITLE I OF THE BILL WILL HAVE A DEFLATIONARY EFFECT BECAUSE IT MAKES AVAILABLE LOWER PRICED GENERIC VERSIONS OF DRUGS. SUCH GENERIC DRUGS ARE THREE TO FIFTEEN TIMES LESS COSTLY THAN THEIR BRAND NAME COUNTER-PARTS. THE ESTIMATED $1 BILLION COST SAVINGS TO CONSUMERS AS A RESULT OF TITLE I'S GENERIC DRUG APPROVAL PROCEDURE WILL HAVE A DEFLATIONARY EFFECT UPON THE NATIONAL ECONOMY. WHILE TITLE II OF THE BILL PROVIDES FOR A LIMITED EXTENSION OF THE PATENTS ON CERTAIN PRODUCTS, THE COMMITTEE BELIEVES THAT THE ADDITIONAL PATENT TERM WILL ACT AS A SPUR TO DEVELOP INNOVATIVE AND, ULTIMATELY, LESS COSTLY TREATMENTS FOR DISEASES.

SECTION-BY-SECTION ANALYSIS

TITLE I-- DRUG PRICE COMPETITION ACT

SECTION 101

SECTION 101 AMENDS SECTION 505 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT (FFDCA) [FN1] TO ESTABLISH A NEW SUBSECTION (J) PROVIDING FOR THE APPROVAL OF ABBREVIATED NEW DRUG APPLICATIONS (ANDA). PAR GRAPH (1) OF SECTION (J) SETS FORTH THE INFORMATION WHICH MUST BE INCLUDED IN AN ANDA.

***21 **2654** ANDA'S FOR DRUGS WHICH ARE THE SAME

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IN THE CASE OF DRUGS WHICH ARE THE SAME AS THE LISTED DRUG, THE FOCUS OF THE BILL IS TO PROVIDE THE FOOD AND DRUG ADMINISTRATION (FDA) WITH SUFFICIENT INFORMATION TO ASSURE THAT THE GENERIC DRUG IS THE SAME AS THE LISTED DRUG [FN2] THAT HAS PREVIOUSLY BEEN DETERMINED TO BE SAFE AND EFFECTIVE. SOME HAVE SUGGESTED THAT A GENERIC DRUG MUST BE IDENTICAL IN ALL RESPECTS TO THE LISTED DRUG INSTEAD OF THE SAME. THE REGULATIONS THAT PERMIT ANDA'S FOR PRE-1962 PIONEER DRUGS MAKE NO SUCH DISTINCTION. [FN3] IN REJECTING THE USE OF THE TERM IDENTICAL, THE FDA REGULATION COMMENTS THAT 'IDENTICAL MEANS A PRODUCT THAT IS THE SAME IN DOSAGE FORM, STRENGTH, AND ROUTE OF ADMINISTRATION, CONTAINS THE SAME ACTIVE INGREDIENT, AND IS RECOMMENDED FOR USE UNDER THE SAME CONDITIONS OF USE.' [FN4] THE COMMITTEE HAS ADOPTED THE FDA'S POLICY OF UTILIZING THE TERM 'SAME' EXCEPT THAT THE BILL PERMITS AN ANDA TO BE APPROVED FOR LESS THAN ALL OF THE INDICATIONS FOR WHICH THE LISTED DRUG HAS BEEN APPROVED AS EXPLAINED BELOW.

FIRST, AN ANDA MUST INCLUDE SUFFICIENT INFORMATION TO SHOW THAT THE CONDITIONS OF USE FOR WHICH THE APPLICANT IS SEEKING APPROVAL ARE THE SAME AS THOSE THAT HAVE BEEN PREVIOUSLY APPROVED FOR THE LISTED DRUG. THE APPLICANT NEED NOT SEEK APPROVAL FOR ALL OF THE INDICATIONS FOR WHICH THE LISTED DRUG HAS BEEN APPROVED. FOR EXAMPLE, IF THE LISTED DRUG HAS BEEN APPROVED FOR HYPERTENSION AND ANGINA PECTORIS, AND IF THE INDICATION FOR HYPERTENSION IS PROTECTED BY PATENT, THEN THE APPLICANT COULD SEEK APPROVAL FOR ONLY THE ANGINA PECTORIS INDICATION.

WHILE THE FDA'S CURRENT REGULATIONS FOR CONSIDERING ANDA'S FOR PIONEER DRUGS APPROVED BEFORE 1962 PERMIT AN APPLICANT TO PETITION FOR APPROVAL FOR AN INDICATION OTHER THAN THAT WHICH HAS BEEN APPROVED FOR THE PIONEER DRUG, SECTION 101 OF THE BILL OVERTURNS THAT POLICY. [FN5] THUS, AN ANDA MAY NOT BE CONSIDERED FOR A CONDITION OF USE THAT HAS NOT BEEN PREVIOUSLY APPROVED FOR THE LISTED DRUG.

AN ANDA MUST ALSO CONTAIN SUFFICIENT INFORMATION TO SHOW THAT THE ACTIVE INGREDIENTS OF THE GENERIC DRUG ARE THE SAME AS THOSE OF THE LISTED DRUG. IF THE LISTED DRUG HAS ONE ACTIVE INGREDIENT, THEN THE ACTIVE INGREDIENT OF THE GENERIC MUST BE THE SAME. IF THE LISTED DRUG HAS MORE THAN ONE ACTIVE INGREDIENT, THEN SUFFICIENT INFORMATION MUST BE INCLUDED TO SHOW THAT ALL OF THE ACTIVE INGREDIENTS IN THE GENERIC DRUG ARE THE SAME.

IN ADDITION, AN ANDA MUST CONTAIN SUFFICIENT INFORMATION TO SHOW THAT THE ROUTE OF ADMINISTRATION, THE DOSAGE FORM AND THE STRENGTH OF THE GENERIC DRUG ARE THE SAME AS THOSE OF THE LISTED DRUG.

FURTHER, AN ANDA MUST INCLUDE SUFFICIENT INFORMATION TO SHOW THAT THE GENERIC DRUG IS BIOEQUIVALENT TO THE LISTED DRUG.

***22 **2655** FIFTH, AN ANDA MUST CONTAIN ADEQUATE INFORMATION TO SHOW THAT THE PROPOSED LABELING FOR THE GENERIC DRUG IS THE SAME AS THAT OF THE LISTED DRUG. THE COMMITTEE RECOGNIZES THAT THE PROPOSED LABELING FOR THE GENERIC DRUG MAY NOT BE EXACTLY THE SAME. FOR EXAMPLE, THE NAME AND ADDRESS OF THE MANUFACTURERS WOULD VARY AS MIGHT THE EXPIRATION DATES FOR THE TWO PRODUCTS. ANOTHER EXAMPLE IS THAT ONE COLOR IS USED IN THE COATING OF THE LISTED DRUG AND ANOTHER COLOR IS USED IN THAT OF THE GENERIC DRUG. THE FDA MIGHT REQUIRE THE LISTED DRUG MAKER TO SPECIFY THE COLOR IN ITS LABEL. THE GENERIC MANUFACTURER, WHICH HAS USED A DIFFERENT COLOR, WOULD HAVE TO SPECIFY A DIFFERENT COLOR IN ITS LABEL.

SIXTH, AN ANDA MUST INCLUDE A LIST OF ALL THE COMPONENTS OF THE GENERIC DRUG, A DESCRIPTION OF THE COMPOSITION OF THE GENERIC DRUG, A DESCRIPTION OF THE METHODS

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AND CONTROLS USED IN THE MANUFACTURE, PROCESSING AND PACKING OF THE GENERIC DRUG, SAMPLES OF THE GENERIC DRUG AND ITS COMPONENTS, AND SPECIMENS OF THE PROPOSED LABELING.

SEVENTH, AN ANDA MUST INCLUDE A CERTIFICATION BY THE APPLICANT REGARDING THE STATUS OF CERTAIN PATENTS APPLICABLE TO THE LISTED DRUG IF THE PATENT INFORMATION HAS BEEN SUBMITTED UNDER SECTION 505(B) OR (C). WITH RESPECT TO ALL PRODUCT PATENTS WHICH CLAIM THE LISTED DRUG AND ALL USE PATENTS WHICH CLAIM AN INDICATION FOR THE DRUG FOR WHICH THE APPLICANT IS SEEKING APPROVAL (HEREAFTER DESCRIBED AS A CONTROLLING USE PATENT), THE APPLICANT MUST CERTIFY, IN HIS OPINION AND TO THE BEST OF HIS KNOWLEDGE, AS TO ONE OF FOUR CIRCUMSTANCES.

THE APPLICANT MAY CERTIFY THAT THE PATENT INFORMATION REQUIRED UNDER SECTIONS 505(B) AND (C) HAS NOT BEEN SUBMITTED IF THAT IS THE CASE. IF APPROPRIATE, THE APPLICANT MAY CERTIFY THAT ONE OR MORE OF THE PRODUCT OR CONTROLLING USE PATENTS PROVIDED HAVE EXPIRED. THIRD, THE APPLICANT MAY CERTIFY WHEN APPROPRIATE THAT ONE OR MORE OF THE PRODUCT OR CONTROLLING USE PATENTS WILL EXPIRE AT SOME SPECIFIED DATE IN THE FUTURE. WHEN THE APPLICANT MAKES THESE CERTIFICATIONS, IT MUST RELY UPON THE PATENT INFORMATION SUPPLIED TO THE FDA. LAST, AN APPLICANT MAY CERTIFY IF APPLICABLE THAT ONE OR MORE OF THE PRODUCT OR CONTROLLING USE PATENTS ARE INVALID OR WILL NOT BE INFRINGED.

THE COMMITTEE RECOGNIZES THAT IN SOME INSTANCES AN APPLICANT WILL HAVE TO MAKE MULTIPLE CERTIFICATIONS WITH RESPECT TO PRODUCT OR CONTROLLING USE PATENTS. FOR EXAMPLE, IF THE PRODUCT PATENT HAS EXPIRED AND A VALID CONTROLLING USE PATENT WILL NOT EXPIRE FOR THREE YEARS, THEN THE APPLICANT MUST CERTIFY THAT ONE PATENT HAS EXPIRED AND THE OTHER WILL EXPIRE IN THREE YEARS. THE COMMITTEE INTENDS THAT THE APPLICANT MAKE THE APPROPRIATE CERTIFICATION FOR EACH PRODUCT AND CONTROLLING USE PATENT.

EIGHTH, IF THERE ARE INDICATIONS WHICH ARE CLAIMED BY ANY USE PATENT AND FOR WHICH THE APPLICANT IS NOT SEEKING APPROVAL, THEN AN ANDA MUST STATE THAT THE APPLICANT IS NOT SEEKING APPROVAL FOR THOSE INDICATIONS WHICH ARE CLAIMED BY SUCH USE PATENT. FOR EXAMPLE, THE LISTED DRUG MAY BE APPROVED FOR TWO INDICATIONS. IF THE APPLICANT IS SEEKING APPROVAL ONLY FOR INDICATION NO. 1, AND NOT INDICATION NO. 2 BECAUSE IT IS PROTECTED BY A USE PATENT, THEN THE APPLICANT MUST MAKE THE APPROPRIATE CERTIFICATION AND A STATEMENT EXPLAINING THAT IT IS NOT SEEKING APPROVAL FOR INDICATION NO. 2.

FINALLY, THE COMMITTEE INTENDS THAT AN ANDA CONTAIN ANY INFORMATION AVAILABLE TO THE APPLICANT REGARDING REPORTS OF ADVERSE EFFECTS**2656 *23 NOT REFLECTED IN THE LABELING, AN ENVIRONMENTAL IMPACT ANALYSIS PURSUANT TO FDA REGULATIONS, STATEMENTS REGARDING THE PROTECTION OF HUMAN SUBJECTS IN CLINICAL INVESTIGATIONS AS REQUIRED BY FDA REGULATIONS, AND A STATEMENT REGARDING COMPLIANCE WITH GOOD LABORATORY PRACTICES IN NON-CLINICAL INVESTIGATIONS AS REQUIRED BY FDA REGULATIONS. [FN6]

ANDA'S FOR DRUGS WHICH ARE DIFFERENT

PARAGRAPH (2)(C) PROHIBITS ANY PERSON FROM SUBMITTING AN ANDA FOR A GENERIC DRUG WHICH DIFFERS FROM THE LISTED DRUG UNLESS THE CHANGE IS PERMITTED BY THE STATUTE AND THE FDA HAS GRANTED A PETITION REQUESTING THE CHANGE.

IF AN APPLICANT WISHES TO VARY THE ROUTE OF ADMINISTRATION, DOSAGE FORM OR

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STRENGTH OF THE GENERIC DRUG FROM THE LISTED DRUG, IT MUST FIRST PETITION THE FDA FOR PERMISSION TO FILE AN ANDA FOR THE DIFFERING GENERIC DRUG. IN ADDITION, AN APPLICANT MAY REQUEST TO VARY ONE OF THE ACTIVE INGREDIENTS IN THE GENERIC DRUG FROM THE LISTED DRUG WHEN THE LISTED DRUG IS A COMBINATION PRODUCT. THE REMAINING ACTIVE INGREDIENTS OF THE GENERIC DRUG MUST BE THE SAME AS THE OTHER ACTIVE INGREDIENTS OF THE LISTED DRUG.

THESE ARE THE ONLY CHANGES FROM THE LISTED DRUG FOR WHICH AN APPLICANT MAY PETITION. AS IS EXPLAINED IN THE ANDA REGULATIONS FOR PRE-1962 DRUGS, THE COMMITTEE GENERALLY EXPECTS THAT APPROVAL OF PETITIONS WILL 'ORDINARILY BE LIMITED TO DOSAGE FORMS FOR THE SAME ROUTE OF ADMINISTRATION OR TO CLOSELY RELATED INGREDIENTS.' [FN7] IF THE FDA GRANTS A PETITION FOR A CHANGE FROM THE LISTED DRUG, THE FDA MAY REQUIRE SUCH ADDITIONAL INFORMATION IN THE ANDA REGARDING THE CHANGE AS IT DEEMS NECESSARY.

THE FDA MUST APPROVE A PETITION TO SUBMIT AN ANDA FOR A DIFFERING GENERIC DRUG UNLESS CLINICAL STUDIES ARE NEEDED TO SHOW THE SAFETY AND EFFECTIVENESS OF THE CHANGE. IN REVIEWING A PETITION TO CHANGE ONE OF THE ACTIVE INGREDIENTS IN A COMBINATION PRODUCT, THE COMMITTEE DOES NOT INTEND TO CHANGE THE FDA'S CURRENT POLICY REGARDING THE EVALUATION OF THE SAFETY AND EFFECTIVENESS OF COMBINATION PRODUCTS. IF THE FDA FINDS THAT SAFETY AND EFFECTIVENESS TESTING OF THE ACTIVE INGREDIENTS OF THE DRUG, INDIVIDUALLY OR IN COMBINATION, IS REQUIRED, THEN THE FDA MUST DENY THE PETITION.

THE FDA MUST EITHER APPROVE OR DISAPPROVE A PETITION WITHIN 90 DAYS OF ITS SUBMISSION. AS IS THE CASE UNDER THE CURRENT REGULATIONS, 'THERE IS NO LEGAL REQUIREMENT THAT THE HEARING OPPORTUNITY PROVIDED BY SECTION 505(C) BE MADE AVAILABLE TO ANDA APPLICANTS WHO DISAGREE WITH AN ADVERSE AGENCY DECISION' ON WHETHER CLINICAL STUDIES ARE NEEDED TO SHOW THE SAFETY AND EFFECTIVENESS OF THE DIFFERING GENERIC DRUG. [FN8] 'APPROPRIATE REVIEW OF SUCH DECISIONS MAY BE HAD . . . UNDER THE APPLICABLE STANDARD-- THAT APPLICABLE TO ADMINISTRATIVE DECISIONMAKING GENERALLY-- WHICH IS WHETHER THE AGENCY'S DECISION IS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW (5 U.S.C. 706(2)(A)).' [FN9] IF THE FDA ***24 ****2657** DOES NOT APPROVE A PETITION, THEN AN ANDA MAY NOT BE FILED FOR A GENERIC DRUG THAT VARIES FROM THE LISTED DRUG.

AN ANDA FOR A DRUG WHICH DIFFERS FROM THE LISTED DRUG AND FOR WHICH A PETITION HAS BEEN APPROVED BY THE FDA MUST CONTAIN SUCH ADDITIONAL INFORMATION REGARDING THE DIFFERENCE AS THE FDA MAY REQUIRE WHEN IT GRANTED THE PETITION. FOR EXAMPLE, IF THE ROUTE OF ADMINISTRATION OF THE GENERIC DRUG DIFFERS FROM THAT OF THE LISTED DRUG, THEN THE FDA MAY REQUIRE SUCH ADDITIONAL INFORMATION ON THAT CHANGE AS IT DEEMS NECESSARY.

IF THE FDA APPROVES A PETITION PERMITTING AN APPLICANT TO VARY ONE OF THE ACTIVE INGREDIENTS OF A GENERIC DRUG FROM THOSE OF THE LISTED COMBINATION DRUG, THE ANDA MUST CONTAIN SUFFICIENT INFORMATION TO SHOW THAT THE ACTIVE INGREDIENTS OF THE GENERIC DRUG (INCLUDING THE VARYING ACTIVE INGREDIENT) ARE OF THE SAME PHARMACOLOGICAL OR THERAPEUTIC CLASS AS THOSE OF THE LISTED DRUG. IN ADDITION, THE DIFFERING GENERIC DRUG MUST BE EXPECTED TO HAVE THE SAME THERAPEUTIC EFFECT WHEN ADMINISTERED TO PATIENTS FOR AN APPROVED CONDITION OF USE.

AN EXAMPLE OF SUCH A CHANGE IN ONE OF THE ACTIVE INGREDIENTS THAT THE FDA MIGHT FIND ACCEPTABLE IS THE SUBSTITUTION OF ACETAMINOPHEN FOR ASPIRIN IN A COMBINATION

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PRODUCT. ANOTHER EXAMPLE MIGHT BE THE SUBSTITUTION OF ONE ANTIHISTAMINE FOR ANOTHER. THE ACTIVE INGREDIENT, WHICH THE APPLICANT WISHES TO VARY AND WHICH THE FDA HAS GRANTED A PETITION, MUST HAVE BEEN APPROVED FOR SAFETY AND EFFECTIVENESS OR MUST NOT BE WITHIN THE REQUIREMENTS OF SECTION 201(P) OF FFDCA. [FN10]

CERTIFICATION OF INVALIDITY OF NONINFRINGEMENT OF A PATENT

WHEN AN APPLICANT CERTIFIES THAT ANY PRODUCT OR CONTROLLING USE PATENT IS INVALID OR WILL NOT BE INFRINGED, PARAGRAPH (2)(B) REQUIRES THAT IT MUST GIVE NOTICE OF SUCH CERTIFICATION TO EITHER THE OWNER OF THE PATENT OR THE REPRESENTATIVE OF THE PATENT OWNER THAT WAS DESIGNATED WHEN THE PATENT INFORMATION WAS SUBMITTED UNDER SECTION 505(B) OR (C) OF THE FFDCA. THE FDA MAY, BY REGULATION, ESTABLISH A PROCEDURE FOR DESIGNATING IN THE NDA THE REPRESENTATIVE OF THE PATENT OWNER. IN ADDITION, NOTICE OF THE CERTIFICATION MUST BE GIVEN TO THE HOLDER OF THE APPROVED NEW DRUG APPLICATION (NDA) FOR THE DRUG WHICH IS CLAIMED BY A PRODUCT PATENT OR THE USE OF WHICH IS CLAIMED BY A USE PATENT.

THIS NOTICE MUST BE GIVEN SIMULTANEOUSLY WITH THE SUBMISSION OF AN ANDA. THE COMMITTEE DOES NOT INTEND THAT APPLICANTS BE PERMITTED TO CIRCUMVENT THIS NOTICE REQUIREMENT BY FILING SHAM ANDA'S OR ANDA'S WHICH ARE SUBSTANTIALLY INCOMPLETE. THE COMMITTEE INTENDS THAT THE APPLICANT MUST HAVE MADE A GOOD FAITH EFFORT TO MEET THE REQUIREMENTS SET FORTH IN PARAGRAPH (2)(A) REGARDING THE CONTENTS OF AN ANDA.

WHILE THE COMMITTEE DOES NOT INTEND THAT FAILURE TO INCLUDE A MINOR PIECE OF INFORMATION IN AN ANDA VITIATES THE EFFECTIVENESS OF THE NOTICE REQUIRED UNDER PARAGRAPH (2)(B), AN ANDA MUST INCLUDE ***25 **2658** THE RESULTS OF ANY REQUIRED BIOAVAILABILITY OR BIOEQUIVALENCE TESTS. FAILURE TO INCLUDE THE RESULTS OF SUCH TESTS WHEN REQUIRED WILL VOID THE EFFECTIVENESS OF ANY NOTICE UNDER PARAGRAPH (2)(B). NOTICE MUST THEN BE GIVEN AGAIN WHEN AN ANDA WITH ANY REQUIRED BIOAVAILABILITY OR BIOEQUIVALENCE DATA IS SUBMITTED TO THE FDA.

WHEN THE APPLICANT GIVES NOTICE OF THE CERTIFICATION OF PATENT INVALIDITY OR NON-INFRINGEMENT, THE NOTICE MUST STATE THAT AN ANDA HAS BEEN SUBMITTED TO OBTAIN APPROVAL OF THE DRUG TO ENGAGE IN THE COMMERCIAL MANUFACTURE, USE OR SALE OF THE GENERIC DRUG BEFORE THE EXPIRATION OF THE PATENT WHICH HAS BEEN CERTIFIED AS INVALID OR NON-INFRINGED.

IF AN ANDA IS AMENDED AFTER SUBMISSION TO INCLUDE A CERTIFICATION THAT A PRODUCT PATENT OR CONTROLLING USE PATENT IS INVALID OR NOT INFRINGED, THEN THE NOTICE OF SUCH CERTIFICATION MUST BE GIVEN TO THE APPROPRIATE PARTIES WHEN THE AMENDED APPLICATION IS SUBMITTED.

GROUNDS FOR DISAPPROVAL OF AN ANDA

PARAGRAPH (3) PROVIDES THAT THE FDA SHALL APPROVE AN ANDA EXCEPT IN ONE OF THE FOLLOWING CIRCUMSTANCES.

FIRST, THE FDA SHALL NOT APPROVE AN ANDA IF THE METHODS USED IN, OR THE FACILITIES AND CONTROLS USED FOR, THE MANUFACTURE, PROCESSING AND PACKING OF THE GENERIC DRUG ARE INADEQUATE TO ASSURE AND PRESERVE ITS IDENTITY, STRENGTH, QUALITY AND PURITY.

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SECOND, AN ANDA SHALL NOT BE APPROVED IF IT DOES NOT CONTAIN ADEQUATE INFORMATION TO SHOW THAT EACH OF THE CONDITIONS FOR USE FOR THE GENERIC DRUG HAVE BEEN PREVIOUSLY APPROVED FOR THE LISTED DRUG. IF AN ANDA INCLUDES A CONDITION FOR USE FOR WHICH THE LISTED DRUG HAS NOT BEEN APPROVED, THEN THE GENERIC DRUG MAY NOT BE APPROVED.

THIRD, AN ANDA MUST BE DISAPPROVED IF THE ACTIVE INGREDIENT OF THE GENERIC DRUG IS NOT THE SAME AS THAT OF THE LISTED DRUG AND THE LISTED DRUG HAS ONLY ONE ACTIVE INGREDIENT. AN ANDA MUST ALSO BE DISAPPROVED IF ANY OF THE ACTIVE INGREDIENTS IN THE GENERIC DRUG ARE NOT THE SAME AS THOSE OF THE LISTED DRUG UNLESS A PETITION REGARDING A CHANGE IN ONE OF THE ACTIVE INGREDIENTS HAS BEEN GRANTED. IF THE LISTED DRUG IS A COMBINATION PRODUCT AND A PETITION PERMITTING A CHANGE IN ONE OF THE ACTIVE INGREDIENTS IN THE GENERIC DRUG HAS BEEN GRANTED, THEN THE ANDA MUST BE DISAPPROVED IF THE OTHER ACTIVE INGREDIENTS OF THE GENERIC DRUG ARE NOT THE SAME AS THOSE OF THE LISTED DRUG. FURTHER, ANDA MUST BE DISAPPROVED IN SUCH A CIRCUMSTANCE IF THE DIFFERENT ACTIVE INGREDIENT IN THE GENERIC DRUG IS NOT A LISTED DRUG OR IF THE DIFFERENT ACTIVE INGREDIENT IS A DRUG WITHIN THE REQUIREMENTS OF SECTION 201(P) OF THE FFDCA.

FOURTH, AN ANDA FOR A DRUG WHICH IS THE SAME MUST BE DISAPPROVED IF IT DOES NOT SHOW THAT THE ROUTE OF ADMINISTRATION, DOSAGE FORM, OR STRENGTH OF THE GENERIC DRUG ARE ALL THE SAME AS THOSE OF THE LISTED DRUG. IF THE ROUTE OF ADMINISTRATION, DOSAGE FORM, OR STRENGTH OF THE GENERIC DRUG DIFFERS FROM THAT OF THE LISTED DRUG, AN ANDA MUST BE DISAPPROVED IF NO PETITION REGARDING THE CHANGE WAS GRANTED.

FIFTH, AN ANDA MUST BE DISAPPROVED IF THE GENERIC DRUG DIFFERS FROM THE LISTED DRUG AND A PETITION REGARDING THE CHANGE HAS BEEN ***26 **2659** GRANTED, BUT THE ANDA DOES NOT CONTAIN ALL OF THE ADDITIONAL INFORMATION THAT THE FDA REQUIRED IN GRANTING THE PETITION.

A SIXTH GROUND REQUIRING DISAPPROVAL OF AN ANDA FOR A GENERIC DRUG WHOSE ACTIVE INGREDIENTS ARE THE SAME AS THOSE OF THE LISTED DRUG IS THAT THERE IS UNSUFFICIENT INFORMATION TO SHOW THAT THE GENERIC DRUG IS BIOEQUIVALENT TO THE LISTED DRUG. IF A PETITION REGARDING A CHANGE IN ONE OF THE ACTIVE INGREDIENTS IN A COMBINATION GENERIC DRUG HAS BEEN GRANTED, THEN THE ANDA MUST BE DISAPPROVED IF THE APPLICATION FAILS TO SHOW THAT THE ACTIVE INGREDIENTS OF THE GENERIC DRUG ARE OF THE SAME PHARMACOLOGICAL OR THERAPEUTIC CLASS AS THOSE OF THE LISTED DRUG. IN ADDITION, SUCH AN ANDA MUST BE DISAPPROVED IF IT FAILS TO SHOW THAT THE DIFFERING GENERIC COMBINATION DRUG CAN BE EXPECTED TO HAVE THE SAME THERAPEUTIC EFFECT AS THE LISTED COMBINATION PRODUCT WHEN ADMINISTERED TO PATIENTS FOR AN APPROVED CONDITION OF USE.

SEVENTH, AN ANDA MUST ALSO BE DISAPPROVED IF IT FAILS TO SHOW THAT THE PROPOSED LABELING FOR THE GENERIC DRUG IS THE SAME AS THAT OF THE LISTED DRUG. CHANGES IN THE PROPOSED LABELING DUE TO THE FACT THAT THE GENERIC DRUG IS PRODUCED OR DISTRIBUTED BY A DIFFERENT MANUFACTURER ARE NOT A GROUNDS FOR DISAPPROVAL. SIMILARLY, CHANGES IN THE PROPOSED LABELING OF THE GENERIC DRUG BECAUSE A PETITION REGARDING A CHANGE HAS BEEN GRANTED IS NOT A GROUNDS FOR DISAPPROVAL.

EIGHTH, AN ANDA MUST BE DISAPPROVED IF IT OR ANY OTHER INFORMATION BEFORE THE FDA SHOWS THAT THE INACTIVE INGREDIENTS OF THE GENERIC DRUG ARE UNSAFE FOR USE UNDER THE CONDITIONS PRESCRIBED, RECOMMENDED, OR SUGGESTED IN THE PROPOSED

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LABELING FOR THE GENERIC DRUG. AN ANDA MUST ALSO BE DISAPPROVED IF THE COMPOSITION OF THE GENERIC DRUG IS UNSAFE UNDER APPROVED CONDITIONS OF USE. FOR EXAMPLE, THE COMPOSITION OF THE GENERIC DRUG MIGHT BE UNSAFE BECAUSE OF THE TYPE OR QUANTITY OF THE INACTIVE INGREDIENT INCLUDED OR BECAUSE OF THE MANNER IN WHICH THE INACTIVE INGREDIENT WAS INCLUDED.

NINTH, AN ANDA MAY NOT BE APPROVED IF THE APPROVAL OF THE LISTED DRUG HAS BEEN WITHDRAWN OR SUSPENDED FOR REASONS OF SAFETY OR EFFECTIVENESS UNDER SECTION 505(E)(1)-(4) OF THE FFDCA. [FN11] THE ANDA MAY ALSO NOT BE APPROVED IF THE FDA DETERMINES THAT THE LISTED DRUG HAS BEEN VOLUNTARILY WITHDRAWN FROM THE MARKET FOR SAFETY OR EFFECTIVENESS REASONS. THE COMMITTEE RECOGNIZES THAT THE MAKER OF A LISTED DRUG MIGHT WITHDRAW IT FROM THE MARKET WITHOUT SPECIFYING THE REASON OR WITHOUT ARTICULATING SAFETY OR EFFECTIVENESS CONCERNS. FOR THIS REASON, THE COMMITTEE AUTHORIZED THE FDA TO EXAMINE WHETHER SAFETY OR EFFECTIVENESS CONCERNS WERE ONE OF THE REASONS FOR THE VOLUNTARY WITHDRAWAL OF THE DRUG FROM THE MARKET. IF THE FDA SO FINDS, THEN AN ANDA FOR A GENERIC VERSION OF THAT DRUG MAY NOT BE APPROVED.

TENTH, AN ANDA MAY NOT BE APPROVED IF IT DOES NOT MEET ANY OF THE REQUIREMENTS SET FORTH IN PARAGRAPH (2)(A). FOR EXAMPLE, AN ANDA THAT DOES NOT CONTAIN THE CERTIFICATIONS REGARDING PATENTS REQUIRED IN PARAGRAPH (A)(A)(VII) CANNOT BE APPROVED.

LAST, AN ANDA MAY NOT BE APPROVED IF IT CONTAINS ANY UNTRUE STATEMENT OF MATERIAL FACT. [FN12]

***27 **2660** APPROVAL OF AN ANDA

PARAGRAPH (4)(A) REQUIRES THE FDA TO APPROVE OR DISAPPROVE AN ANDA WITHIN 180 DAYS OF INITIAL RECEIPT OF THE APPLICATION. THE COMMITTEE RECOGNIZES THAT EXTENSIONS MAY BE NECESSARY SO THE BILL PERMITS EXTENSIONS OF THIS PERIOD FOR SO LONG AS THE APPLICANT AND THE FDA MAY AGREE UPON.

EFFECTIVENESS OF AN ANDA APPROVAL

THE COMMITTEE RECOGNIZES THAT SOME ANDA'S WILL BE SUBMITTED AND READY FOR APPROVAL BEFORE THE PATENT ON THE LISTED DRUG HAS EXPIRED. TO DEAL WITH THIS SITUATION AND TO ASSURE THAT THE FDA CONCERNS ITSELF SOLELY WITH THE SAFETY AND EFFECTIVENESS OF THE GENERIC DRUG, PARAGRAPH (4)(B) PERMITS THE FDA TO APPROVE AN ANDA BUT MAKE THE APPROVAL EFFECTIVE AT SOME LATER DATE WHEN APPROPRIATE.

IF THE APPLICANT CERTIFIED IN AN ANDA THAT NO PATENT INFORMATION WAS SUPPLIED OR THAT THE RELEVANT PATENTS HAVE EXPIRED, THEN THE APPROVAL OF THE ANDA MAY BE MADE EFFECTIVE IMMEDIATELY. IF THE APPLICANT CERTIFIED BASED UPON THE SUBMITTED PATENT INFORMATION THAT THE PATENT OR PATENTS WOULD EXPIRE IN ONE YEAR, THEN AN ANDA MAY BE APPROVED AND THE APPROVAL MADE EFFECTIVE IN ONE YEAR.

IF THE APPLICANT CERTIFIED THAT ONE OR MORE OF THE PRODUCT OR CONTROLLING USE PATENTS WERE INVALID OR NOT INFRINGED, THEN APPROVAL OF THE ANDA MAY BE MADE EFFECTIVE IMMEDIATELY EXCEPT IN THE FOLLOWING SITUATION. IF WITHIN 45 DAYS AFTER NOTICE OF THE CERTIFICATION OF INVALIDITY OR NON-INFRINGEMENT IS RECEIVED, AN ACTION FOR PATENT INFRINGEMENT REGARDING ONE OR MORE OF THE PATENTS SUBJECT TO THE

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CERTIFICATION IS BROUGHT, [FN13] THEN APPROVAL OF THE ANDA MAY NOT BE MADE EFFECTIVE IMMEDIATELY. INSTEAD, APPROVAL OF THE ANDA MAY NOT BE MADE EFFECTIVE UNTIL 18 MONTHS AFTER THE NOTICE OF THE CERTIFICATION WAS PROVIDED UNLESS A DISTRICT COURT HAS DECIDED A CASE FOR PATENT INFRINGEMENT EARLIER. ONCE EITHER OF THESE EVENTS OCCURS AND THE APPROVAL OF THE ANDA BECOMES EFFECTIVE, THEN THE FDA HAS DISCHARGED ITS STATUTORY RESPONSIBILITY WITH RESPECT TO MAKING THE APPROVAL OF THE GENERIC DRUG EFFECTIVE.

EACH PARTY TO THE ACTION HAS AN AFFIRMATIVE DUTY TO REASONABLY COOPERATE IN EXPEDITING THE ACTION. IF THE PLAINTIFF BREACHES THAT DUTY, THE COURT MAY SHORTEN THE 18 MONTH PERIOD AS IT DEEMS APPROPRIATE. IF THE DEFENDANT BREACHES THAT DUTY, THE COURT MAY EXTEND THE 18 MONTH PERIOD AS IT DEEMS APPROPRIATE.

IF THE COURT DECIDES THAT THE PATENT IS INVALID OR NOT INFRINGED BEFORE THE EXPIRATION OF THE 18 MONTH PERIOD (OR SUCH SHORTER OR LONGER PERIOD AS THE COURT DECIDES), THEN THE APPROVAL MAY BE MADE EFFECTIVE ON THE DATE OF THE COURT DECISION. IF THE COURT DECIDES THAT THE PATENT IS VALID OR INFRINGED BEFORE THE EXPIRATION OF THE 18 MONTH PERIOD, THEN THE APPROVAL MAY BE MADE EFFECTIVE ON SUCH DATA AS THE COURT ORDERS. THE COMMITTEE WISHES TO EMPHASIZE THAT THE COURT MAY NOT ORDER AN ANDA APPROVED UNDER THIS PROVISION. ***28 **2661** THESE ARE TIMES WHEN APPROVAL OF AN ANDA MAY BE MADE EFFECTIVE IF THE FDA HAS APPROVED THE ANDA.

THIS ADDITIONAL REMEDY PERMITS THE COMMENCEMENT OF A LEGAL ACTION FOR PATENT INFRINGEMENT BEFORE THE GENERIC DRUG MAKER HAS BEGUN MARKETING. THE COMMITTEE BELIEVES THIS PROCEDURE FAIRLY BALANCES THE RIGHTS OF A PATENT OWNER TO PREVENT OTHERS FROM MAKING, USING, OR SELLING ITS PATENTED PRODUCT AND THE RIGHTS OF THIRD PARTIES TO CONTEST THE VALIDITY OF A PATENT OR TO MARKET A PRODUCT WHICH THEY BELIEVE IS NOT CLAIMED BY THE PATENT.

THE PROVISIONS OF THIS BILL RELATING TO THE LITIGATION OF DISPUTES INVOLVING PATENT VALIDITY AND INFRINGEMENT ARE NOT INTENDED TO MODIFY EXISTING PATENT LAW WITH RESPECT TO THE BURDEN OF PROOF AND THE NATURE OF THE PROOF TO BE CONSIDERED BY THE COURTS IN DETERMINING WHETHER A PATENT IS VALID OR INFRINGED.

CONCERN HAS BEEN EXPRESSED THAT PERMITTING AN APPLICANT TO MARKET ITS DRUG AT THE CONCLUSION OF THE 18 MONTH PERIOD AND POSSIBLY BEFORE THE RESOLUTION OF THE PATENT INFRINGEMENT SUIT OVERTURNS THE STATUTORY PRESUMPTION OF A PATENT'S VALIDITY. ON THE CONTRARY, THE COMMITTEE INTENDS THAT A PATENT WOULD HAVE THE SAME STATUTORY PRESUMPTION OF VALIDITY AS IS AFFORDED UNDER CURRENT LAW.

IN MOST INSTANCES, AN ANDA WILL CONTAIN MULTIPLE CERTIFICATIONS. THE FDA SHOULD MAKE APPROVAL OF THE ANDA EFFECTIVE UPON THE LAST CERTIFICATION. FOR EXAMPLE, IF AN ANDA CONTAINS A CERTIFICATION THAT A PRODUCT PATENT IS EXPIRED AND A CONTROLLING USE PATENT WILL EXPIRE IN THREE YEARS, THEN THE FDA MUST MAKE APPROVAL OF THE ANDA EFFECTIVE IN THREE YEARS. IN THE CASE WHERE THE PATENT CERTIFICATION IS AMENDED IN AN ANDA TO ALLEGE INVALIDITY OR NON-INFRINGEMENT OF A PATENT, THE FDA MAY NOT MAKE THE APPROVAL EFFECTIVE WITHIN THE 45 DAY PERIOD THAT AN ACTION FOR PATENT INFRINGEMENT MAY BE BROUGHT.

NO ACTION FOR A DECLARATORY JUDGMENT REGARDING THE PATENT AT ISSUE MAY BE BROUGHT BEFORE THE EXPIRATION OF THE 45 DAY PERIOD COMMENCING WITH THE PROVISION OF NOTICE OF THE CERTIFICATION OF PATENT INVALIDITY OR NON-INFRINGEMENT. ANY SUIT FOR DECLARATORY JUDGMENT AFTER THE 45 DAY PERIOD MUST BE BROUGHT IN THE JUDICIAL DISTRICT WHERE THE DEFENDANT HAS ITS PRINCIPAL OF BUSINESS OR A REGULAR AND

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ESTABLISHED PLACE OF BUSINESS.

SUBSEQUENT ANDA'S CERTIFYING PATENT INVALIDITY OR NONINFRINGEMENT

IF AN ANDA CERTIFYING PATENT INVALIDITY OR NON-INFRINGEMENT IS FILED SUBSEQUENT TO AN ANDA FOR THE SAME LISTED DRUG THAT HAS MADE THE SAME CERTIFICATION OF INVALIDITY OR NON-INFRINGEMENT, PARAGRAPH (4)(B)(IV) PROVIDES THAT THE APPROVAL OF THE SUBSEQUENT ANDA MAY NOT BE MADE EFFECTIVE SOONER THAN 180 DAYS AFTER THE PREVIOUS APPLICANT HAS BEGUN COMMERCIAL MARKETING, OR THE DATE ON WHICH THE COURT HOLDS THE PATENT INVALID OR NOT INFRINGED, WHICHEVER OCCURS FIRST. IN THE EVENT OF MULTIPLE ANDA'S CERTIFYING PATENT INVALIDITY OR NON-INFRINGEMENT, THE COURTS SHOULD EMPLOY THE EXISTING RULES FOR MULTIDISTRICT LITIGATION, WHEN APPROPRIATE, TO AVOID HARDSHIP ON THE PARTIES AND WITNESSES AND TO PROMOTE THE JUST AND EFFICIENT CONDUCT OF THE PATENT INFRINGEMENT ACTIONS. [FN14]

***29 **2662** DISAPPROVAL OF AN ANDA

IF THE FDA DECIDES TO DISAPPROVE AN ANDA, PARAGRAPH (4)(C) PROVIDES THAT THE FDA MUST GIVE THE APPLICANT NOTICE OF THE OPPORTUNITY FOR A HEARING ON THE ISSUE OF THE APPROVABILITY OF THE ANDA. TO AVAIL ITSELF OF THIS HEARING, THE APPLICANT MUST SUBMIT A WRITTEN REQUEST WITHIN 30 DAYS OF THE NOTICE. IF A HEARING IS REQUESTED, IT MUST BEGIN NOT LATER THAN 120 DAYS AFTER THE NOTICE. HOWEVER, THE HEARING MAY BE HELD LATER IF BOTH THE APPLICANT AND THE FDA AGREE. THE HEARING SHALL BE CONDUCTED ON AN EXPEDITED BASIS. THE FDA'S ORDER REGARDING THE HEARING SHALL BE ISSUED WITHIN 90 DAYS AFTER THE DATE FOR FILING FINAL BRIEFS.

TRANSITION RULE

PARAGRAPH (4)(D)(I) PROVIDES THAT THE FDA MAY NOT MAKE EFFECTIVE THE APPROVAL OF AN ANDA FOR A DRUG INCLUDING AN ACTIVE INGREDIENT (INCLUDING ANY ESTER OR SALT OF THE ACTIVE INGREDIENT) WHICH WAS APPROVED FOR THE FIRST TIME IN AN NDA BETWEEN JANUARY 1, 1982 AND THE DATE OF ENACTMENT OF THIS BILL UNTIL 10 YEARS AFTER THE DATE OF APPROVAL OF THE NDA. FOR EXAMPLE, IF ACTIVE INGREDIENT X WAS APPROVED IN A DRUG FOR THE FIRST TIME IN 1983, WHEN THE APPROVAL OF AN ANDA FOR A DRUG CONTAINING ACTIVE INGREDIENT X COULD NOT BE MADE EFFECTIVE UNTIL 1993.

UNPATENTABLE DRUGS

IF THE ACTIVE INGREDIENT (INCLUDING ANY ESTER OR SALT OF THE ACTIVE INGREDIENT) OF A DRUG IS APPROVED FOR THE FIRST TIME IN AN NDA AFTER THE ENACTMENT OF THIS BILL, THEN PARAGRAPH (4)(D)(II) PROVIDES THAT THE FDA MAY NOT MAKE THE APPROVAL OF AN ANDA FOR A DRUG WHICH CONTAINS THE SAME ACTIVE INGREDIENT EFFECTIVE UNTIL FOUR YEARS AFTER THE APPROVAL OF THE NDA IF THE FOLLOWING CONDITIONS ARE MET.

FIRST, THE HOLDER OF THE NDA MUST CERTIFY THAT NO PATENT HAS EVER BEEN ISSUED TO ANY PERSON FOR SUCH DRUG, OR FOR A METHOD OF USING SUCH DRUG. SECOND, THE HOLDER MUST CERTIFY THAT IT CANNOT RECEIVE A PATENT FOR SUCH DRUG OR FOR A METHOD USING SUCH DRUG FOR ANY KNOWN THERAPEUTIC PURPOSE. IN DETERMINING WHETHER A DRUG MEETS

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THESE TWO PATENT STIPULATIONS, THE FDA MAY RELY UPON THE CERTIFICATIONS OF THE NDA HOLDER.

IF THE FDA DETERMINES AT ANY TIME DURING THE FOUR YEAR PERIOD THAT AN ADEQUATE SUPPLY OF THE DRUG WILL NOT BE AVAILABLE, IT MAY MAKE THE APPROVAL OF AN ANDA EFFECTIVE BEFORE THE EXPIRATION OF THE FOUR YEAR PERIOD. THE FDA MAY ALSO MAKE THE APPROVAL OF AN ANDA FOR SUCH DRUG EFFECTIVE BEFORE THE FOUR YEAR PERIOD IF THE HOLDER OF THE NDA CONSENTS.

WITHDRAWAL OR SUSPENSION OF LISTED DRUG'S APPROVAL

PARAGRAPH (5) PROVIDES THAT THE APPROVAL OF AN ANDA IS WITHDRAWN OR SUSPENDED IF APPROVAL OF THE LISTED VERSION OF THE GENERIC DRUG HAS BEEN WITHDRAWN OR SUSPENDED FOR SAFETY OR EFFECTIVENESS REASONS AS SET FORTH IN SECTION 505(E)(1)-(4) OF THE FFDCA. THE APPROVAL OF AN ANDA IS ALSO WITHDRAWN OR SUSPENDED IF IT REFERS TO A DRUG WHOSE APPROVAL IS WITHDRAWN OR SUSPENDED UNDER SECTION 505(J)(5) OF THE FFDCA. IN ADDITION, THE APPROVAL OF AN ANDA IS WITHDRAWN OR SUSPENDED IF THE FDA DETERMINES THAT THE LISTED ***30 **2663** DRUG HAS BEEN VOLUNTARILY WITHDRAWN FROM SALE DUE TO SAFETY OR EFFECTIVENESS CONCERNS.

THE COMMITTEE RECOGNIZES THAT THE MAKER OF A LISTED DRUG MIGHT WITHDRAW IT FROM THE MARKET WITHOUT SPECIFYING THE REASON OR WITHOUT ARTICULATING SAFETY OR EFFECTIVENESS CONCERNS. FOR THIS REASON, THE COMMITTEE AUTHORIZED THE FDA TO EXAMINE WHETHER SAFETY OR EFFECTIVENESS CONCERNS WERE ONE OF THE REASONS FOR THE VOLUNTARY WITHDRAWAL OF THE DRUGS FROM THE MARKET. IF THE FDA SO FINDS, THEN THE APPROVAL OF AN ANDA FOR A GENERIC VERSION OF THAT DRUG MUST BE WITHDRAWN OR SUSPENDED.

THE ANDA MUST BE WITHDRAWN OR SUSPENDED FROM SALE FOR THE SAME PERIOD AS THE APPROVAL OF THE DRUG TO WHICH IT REFERS HAS BEEN WITHDRAWN OR SUSPENDED. WHEN THE LISTED DRUG HAS BEEN VOLUNTARILY WITHDRAWN FROM THE MARKET AND THE FDA HAS DETERMINED THAT THE LISTED DRUG WAS WITHDRAWN DUE TO SAFETY OR EFFECTIVENESS REASONS, THEN THE APPROVAL OF THE ANDA MUST BE WITHDRAWN UNTIL SUCH TIME AS THE FDA DETERMINES THAT THE LISTED DRUG WAS NOT WITHDRAWN FROM SALE FOR SAFETY OR EFFECTIVENESS REASONS.

LISTINGS OF DRUGS

WITHIN 60 DAYS AFTER ENACTMENT OF THIS BILL, PARAGRAPH (6) REQUIRES THE FDA TO PUBLISH AND TO MAKE AVAILABLE A LIST OF DRUGS ELIGIBLE FOR CONSIDERATION IN AN ANDA. THE LIST MUST INCLUDE THE OFFICIAL AND PROPRIETARY NAME OF EACH DRUG THAT HAS BEEN APPROVED FOR SAFETY AND EFFECTIVENESS PRIOR TO THE DATE OF ENACTMENT OF THE BILL. THE LIST MUST BE IN ALPHABETICAL ORDER. IF THE DRUG WAS APPROVED AFTER 1981, THE LIST MUST INCLUDE THE DATE OF APPROVAL OF THE DRUG AND THE NDA NUMBER. THIRD, THE LIST MUST SPECIFY WHETHER IN VITRO OR IN VIVO BIOEQUIVALENCE STUDIES, OR BOTH, ARE REQUIRED FOR ANDA'S.

AT 30-DAY INTERVALS, THE FDA MUST UPDATE THE LIST TO INCLUDE DRUGS THAT HAVE BEEN APPROVED FOR SAFETY AND EFFECTIVENESS AFTER ENACTMENT OF H.R. 3605 AND DRUGS APPROVED IN ANDA'S UNDER THIS SUBSECTION. IN ADDITION, THE FDA MUST INTEGRATE INTO THE LIST PATENT INFORMATION SUBMITTED UNDER SECTIONS 505(B) AND (C) OF THE

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FFDCA AS IT BECOMES AVAILABLE.

A DRUG APPROVED FOR SAFETY AND EFFECTIVENESS UNDER SECTION 505(C) OR UNDER SUBSECTION (J) SHALL BE CONSIDERED AS PUBLISHED AND THUS ELIGIBLE FOR APPROVAL IN AN ANDA ON THE DATE OF ITS APPROVAL OR THE DATE OF ENACTMENT, WHICHEVER IS LATER.

PARAGRAPH (6)(C) PROVIDES A DRUG MAY NOT BE LISTED AS ELIGIBLE FOR CONSIDERATION IN AN ANDA IF THE APPROVAL OF THE PIONEER DRUG IS WITHDRAWN OR SUSPENDED FOR SAFETY OR EFFECTIVENESS REASONS AS SET FORTH IN SECTION 505(E)(1)-(4) OF THE FFDCA OR IF APPROVAL OF THE GENERIC DRUG WAS WITHDRAWN OR SUSPENDED UNDER SECTION 505(J)(5) OF THE FFDCA. IN ADDITION, A DRUG MAY NOT BE LISTED IF THE FDA DETERMINES THAT THE DRUG HAS BEEN VOLUNTARILY WITHDRAWN FROM SALE DUE TO SAFETY OR EFFECTIVENESS CONCERNS. IF SUCH A DRUG HAS ALREADY BEEN LISTED, THEN IT MUST BE IMMEDIATELY REMOVED FROM THE LIST.

THE COMMITTEE RECOGNIZES THAT THE MAKER OF A LISTED DRUG MIGHT WITHDRAW IT FROM THE MARKET WITHOUT SPECIFYING THE REASON OF WITHOUT ARTICULATING SAFETY OR EFFECTIVENESS CONCERNS. FOR THIS REASON, THE COMMITTEE AUTHORIZED THE FDA TO EXAMINE WHETHER SAFETY OR EFFECTIVENESS CONCERNS WERE ONE OF THE REASONS FOR THE VOLUNTARY WITHDRAWAL OF THE DRUGS FROM THE MARKET. IF THE FDA SO FINDS, THEN ***31 **2664** THE DRUG MAY NOT BE LISTED. PERSONS ADVERSELY AFFECTED BY THIS DECISION MAY SEEK JUDICIAL REVIEW UNDER TITLE 5 OF THE UNITED STATES CODE.

A DRUG MAY NOT BE LISTED AS LONG AS ITS APPROVAL IS WITHDRAWN OR SUSPENDED. IF THE DRUG HAS BEEN VOLUNTARILY WITHDRAWN FROM THE MARKET, THEN THE DRUG MAY NOT BE LISTED UNTIL THE FDA DETERMINES THAT THE DRUG WAS NOT WITHDRAWN FROM SALE FOR SAFETY OR EFFECTIVENESS REASONS. A NOTICE REGARDING THE REMOVAL OF ANY DRUG FROM THE LIST MUST BE PUBLISHED IN THE FEDERAL REGISTER.

BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

AS USED IN THIS BILL, THE TERM 'BIOAVAILABILITY' MEANS THE RATE AND EXTENT TO WHICH THE ACTIVE INGREDIENT OR THERAPEUTIC INGREDIENT IS ABSORBED FROM A DRUG AND BECOMES AVAILABLE AT THE SITE OF DRUG ACTION. [FN15]

A DRUG SHALL BE CONSIDERED BIOEQUIVALENT TO A LISTED DRUG IF THE RATE AND EXTENT OF ABSORPTION OF THE GENERIC DRUG DO NOT SHOW A SIGNIFICANT DIFFERENCE FROM THE RATE AND EXTENT OF ABSORPTION OF THE LISTED DRUG WHEN ADMINISTERED AT THE SAME MOLAR DOSE OF THE THERAPEUTIC INGREDIENT UNDER SIMILAR EXPERIMENTAL CONDITIONS IN EITHER A SINGLE DOSE OR MULTIPLE DOSES. A GENERIC DRUG SHALL ALSO BE CONSIDERED TO BE BIOEQUIVALENT TO A LISTED DRUG IF THE EXTENT OF ABSORPTION OF THE GENERIC DRUG DOES NOT SHOW A SIGNIFICANT DIFFERENCE FROM THE EXTENT OF ABSORPTION OF THE LISTED DRUG WHEN ADMINISTERED AT THE SAME MOLAR DOSE OF THE THERAPEUTIC INGREDIENT UNDER SIMILAR EXPERIMENTAL CONDITIONS IN EITHER A SINGLE DOSE OR MULTIPLE DOSES AND THE DIFFERENCE FROM THE LISTED DRUG IN THE RATE OF ABSORPTION OF THE GENERIC DRUG IS INTENTIONAL, IS REFLECTED IN THE PROPOSED LABELING, IS NOT ESSENTIAL TO THE ATTAINMENT OF EFFECTIVE BODY DRUG CONCENTRATIONS ON CHRONIC USE, AND IS CONSIDERED MEDICALLY INSIGNIFICANT FOR THE DRUG. [FN16]

SECTION 102

SECTION 102 OF THE BILL REQUIRES THAT CERTAIN PATENT INFORMATION BE FILED WITH

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ALL NEW NDA'S AND WITH ALL NDA'S PREVIOUSLY FILED BUT NOT YET APPROVED. PENDING AND FUTURE NDA'S MAY NOT BE APPROVED UNLESS THEY CONTAIN THE APPROPRIATE PATENT INFORMATION. THE FDA SHALL PUBLISH THE PATENT INFORMATION UPON APPROVAL OF THE NDA.

THIS SECTION ALSO REQUIRES THAT ANY PREVIOUSLY APPROVED NDA BE AMENDED WITHIN 30 DAYS OF ENACTMENT OF THIS BILL TO INCLUDE CERTAIN PATENT INFORMATION. THE FDA SHALL PUBLISH THE PATENT INFORMATION UPON ITS SUBMISSION. AN NDA MAY BE REVOKED IF THE PATENT INFORMATION AVAILABLE IS ADVISABLE AND IS NOT FILED WITHIN 30 DAYS AFTER RECEIPT OF A WRITTEN NOTICE FROM THE FDA SPECIFYING THE FAILURE TO PROVIDE THE PATENT INFORMATION.

THE PATENT INFORMATION TO BE FILED INCLUDES THE PATENT NUMBER AND THE EXPIRATION DATE OF ANY PATENT WHICH CLAIMS THE DRUG IN THE NDA OR WHICH CLAIMS A METHOD OF USING SUCH DRUG WITH RESPECT TO WHICH A CLAIM OF PATENT INFRINGEMENT COULD REASONABLY BE ASSERTED ***32 **2665** IF A PERSON NOT LICENSED BY THE OWNER ENGAGED IN THE MANUFACTURE, SALE OR USE OF THE DRUG. PATENTS WHICH CLAIM A METHOD OF MANUFACTURING SUCH DRUG ARE NOT REQUIRED TO BE SUBMITTED.

FINALLY, SECTION 102 MAKES A NUMBER OF TECHNICAL CHANGES.

SECTION 103

SECTION 103 AMENDS SECTION 505(B) OF THE FFDCA TO REQUIRE AN APPLICANT FILING A PAPER NDA'S FOR A LISTED DRUG UNDER SECTION 505(J)(6) TO MAKE THE SAME CERTIFICATIONS REGARDING PATENTS AS MANDATED IN THE FILING OF ANDA'S UNDER NEW SUBSECTION (J) OF THE FFDCA. IN ADDITION, THE FDA MUST MAKE APPROVALS FOR SUCH PAPER NDA'S EFFECTIVE UNDER THE SAME CONDITIONS THAT APPLY TO ANDA'S SUBMITTED UNDER SUBSECTION (J). FINALLY, SECTION 103 APPLIES THE 10 YEAR TRANSITION RULE AND THE 4 YEAR UNPATENTABLE SUBSTANCES RULE TO PAPER NDA'S.

PAPER NDA'S

PAPER NDA'S ARE DEFINED AS ANY APPLICATION SUBMITTED UNDER SECTION 505(B) OF THE FFDCA IN WHICH THE INVESTIGATIONS RELIED UPON BY THE APPLICANT TO SHOW SAFETY AND EFFECTIVENESS WERE NOT CONDUCTED BY OR FOR THE APPLICANT AND THE APPLICANT HAS NOT OBTAINED A RIGHT OF REFERENCE OR USE FROM THE PERSON WHO CONDUCTED THE STUDIES OR FOR WHOM THE STUDIES WERE CONDUCTED.

PATENT CERTIFICATIONS IN PAPER NDA'S FOR LISTED DRUGS

WHEN A PAPER NDA'S IS SUBMITTED FOR A LISTED DRUG UNDER SECTION 505(J)(6), IT MUST INCLUDE A CERTIFICATION BY THE APPLICANT REGARDING THE STATUS OF CERTAIN PATENTS APPLICABLE TO THE LISTED DRUG IF SUCH INFORMATION HAS BEEN PROVIDED TO THE FDA. WITH RESPECT TO ALL PRODUCT PATENTS WHICH CLAIM THE LISTED DRUG AND ALL USE PATENTS WHICH CLAIM AN INDICATION FOR THE DRUG FOR WHICH THE APPLICANT IS SEEKING APPROVAL (HEREAFTER DESCRIBED AS A CONTROLLING USE PATENT), THE APPLICANT MUST CERTIFY, IN HIS OPINION AND TO THE BEST OF HIS KNOWLEDGE, AS TO ONE OF FOUR CIRCUMSTANCES.

FIRST, THE APPLICANT MAY CERTIFY THAT THE PATENT INFORMATION REQUIRED UNDER

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SECTIONS 505(B) AND (C) HAS NOT BEEN SUBMITTED IF THAT IS THE CASE. SECOND, IF APPROPRIATE, THE APPLICANT MAY CERTIFY THAT ONE OR MORE OF THE PRODUCT OR CONTROLLING USE PATENTS WILL EXPIRE AT SOME SPECIFIED DATE IN THE FUTURE. WHEN THE APPLICANT MAKES THESE CERTIFICATIONS, IT MUST RELY UPON THE PATENT INFORMATION SUPPLIED TO THE FDA. LAST, AN APPLICANT MAY CERTIFY IF APPLICABLE THAT ONE OR MORE OF THE PRODUCT OR CONTROLLING USE PATENTS ARE INVALID OR WILL NOT BE INFRINGED.

THE COMMITTEE RECOGNIZES THAT IN SOME INSTANCES AN APPLICANT WILL HAVE TO MAKE MULTIPLE CERTIFICATIONS WITH RESPECT TO PRODUCT AND CONTROLLING USE PATENTS. FOR EXAMPLE, IF THE PRODUCT PATENT HAS EXPIRED AND VALID CONTROLLING USE PATENT WILL NOT EXPIRE FOR THREE YEARS, THEN THE APPLICANT MUST CERTIFY THAT ONE PATENT HAS EXPIRED AND THE OTHER WILL EXPIRE IN THREE YEARS. THE COMMITTEE INTENDS THAT THE APPLICANT MAKE THE APPROPRIATE CERTIFICATION FOR EACH PRODUCT AND CONTROLLING USE PATENT.

***33 **2666** EVERY PAPER NDA FOR A LISTED DRUG MUST ALSO STATE, WHEN APPLICABLE, THAT THE APPLICANT IS NOT SEEKING APPROVAL FOR AN INDICATION WHICH IS CLAIMED BY ANY USE PATENT FOR WHICH IT HAS NOT MADE A CERTIFICATION. FOR EXAMPLE, THE LISTED DRUG MAY BE APPROVED FOR TWO INDICATIONS. IF THE APPLICANT IS SEEKING APPROVAL ONLY FOR INDICATION NO. 1, AND NOT INDICATION NO. 2 BECAUSE IT IS PROTECTED BY A USE PATENT, THEN THE APPLICANT MUST MAKE THE APPROPRIATE CERTIFICATIONS AND A STATEMENT EXPLAINING THAT IT IS NOT SEEKING APPROVAL FOR INDICATION NO. 2.

CERTIFICATION OF INVALIDITY OR NONINFRINGEMENT OF A PATENT

WHEN AN APPLICANT CERTIFIES THAT ANY PRODUCT OR CONTROLLING USE PATENT IS INVALID OR WILL NOT BE INFRINGED, SECTION 505(B)(3) REQUIRES THAT IT MUST GIVE NOTICE OF SUCH CERTIFICATION TO EITHER THE OWNER OF THE PATENT OR THE REPRESENTATIVE OF THE PATENT OWNER THAT WAS SO DESIGNATED WHEN THE PATENT INFORMATION WAS SUBMITTED UNDER SECTION 505(B) OR (C) OF THE FFDCA. THE FDA MAY, BY REGULATION, ESTABLISH A PROCEDURE FOR DESIGNATING IN THE NDA THE REPRESENTATIVE OF THE PATENT OWNER. IN ADDITION, NOTICE OF THE CERTIFICATION MUST BE GIVEN TO THE HOLDER OF THE APPROVED NEW DRUG APPLICATION (NDA) FOR THE DRUG WHICH IS CLAIMED BY THE PRODUCT PATENT OR THE USE OF WHICH IS CLAIMED BY THE USE PATENT.

THIS NOTICE MUST BE GIVEN SIMULTANEOUSLY WITH THE SUBMISSION OF A PAPER NDA. THE COMMITTEE DOES NOT INTEND THAT APPLICANTS BE PERMITTED TO CIRCUMVENT THIS NOTICE REQUIREMENT BY FILING SHAM PAPER NDA'S OR PAPER NDA'S WHICH ARE SUBSTANTIALLY INCOMPLETE. THE COMMITTEE INTENDS THAT THE APPLICANT MUST HAVE MADE A GOOD FAITH EFFORT TO MEET THE REQUIREMENTS REGARDING THE CONTENTS OF A PAPER NDA AS SET FORTH IN SECTION 505(B) OF FFDCA.

WHEN THE APPLICANT GIVES NOTICE OF THE CERTIFICATION OF INVALIDITY OR NON-INFRINGEMENT, THE NOTICE MUST STATE THAT A PAPER NDA HAS BEEN SUBMITTED TO OBTAIN APPROVAL OF THE DRUG TO ENGAGE IN THE COMMERCIAL MANUFACTURE, USE OF SALE OF THE GENERIC DRUG BEFORE THE EXPIRATION OF THE PATENT WHICH HAS BEEN CERTIFIED AS INVALID OR NON-INFRINGED.

IF A PAPER NDA IS AMENDED AFTER SUBMISSION TO INCLUDE A CERTIFICATION THAT A PRODUCT PATENT OR CONTROLLING USE PATENT IS INVALID, THEN THE NOTICE OF SUCH CERTIFICATION MUST BE GIVEN TO THE APPROPRIATE PARTIES WHEN THE AMENDED

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APPLICATION IS SUBMITTED.

EFFECTIVENESS OF APPROVAL OF A PAPER NDA FOR A LISTED DRUG

THE COMMITTEE RECOGNIZES THAT SOME PAPER NDA'S FOR LISTED DRUGS WILL BE SUBMITTED AND READY FOR APPROVAL BEFORE THE PATENT ON THE LISTED DRUG HAS EXPIRED. TO DEAL WITH THIS SITUATION AND TO ASSURE THAT THE FDA CONCERNS ITSELF SOLELY WITH THE SAFETY AND EFFECTIVENESS OF THE GENERIC DRUG, SECTION 505(C)(3) REQUIRES THE FDA TO APPROVE A PAPER NDA BUT MAKE THE APPROVAL EFFECTIVE AT SOME LATER DATE WHEN APPROPRIATE.

IF THE APPLICANT CERTIFIED IN THE PAPER NDA THAT NO PATENT INFORMATION WAS SUPPLIED OR THAT THE RELEVANT PATENTS HAVE EXPIRED, THEN THE APPROVAL OF THE PAPER NDA MAY BE MADE EFFECTIVE IMMEDIATELY. IF THE APPLICANT CERTIFIED BASED UPON THE SUBMITTED PATENT INFORMATION THAT THE PATENT WOULD EXPIRE IN ONE YEAR, THEN THE ***34 **2667** PAPER NDA MAY BE APPROVED AND THE APPROVAL MADE EFFECTIVE IN ONE YEAR.

IF THE APPLICANT CERTIFIED THAT ONE OR MORE OF THE PRODUCT OF CONTROLLING USE PATENTS WERE INVALID OR NOT INFRINGED, THEN APPROVAL OF THE PAPER NDA MAY BE MADE EFFECTIVE IMMEDIATELY EXCEPT IN THE FOLLOWING SITUATION. IF WITHIN 45 DAYS AFTER NOTICE OF THE CERTIFICATION OF INVALIDITY OR NON-INFRINGEMENT IS RECEIVED, AN ACTION FOR PATENT INFRINGEMENT REGARDING ONE OR MORE OF THE PATENT SUBJECT TO THE CERTIFICATION IS BROUGHT, [FN17] THEN APPROVAL OF THE PAPER NDA MAY NOT BE MADE EFFECTIVE IMMEDIATELY. INSTEAD, APPROVAL OF THE PAPER NDA MAY NOT BE MADE EFFECTIVE UNTIL 18 MONTHS AFTER THE NOTICE OF THE CERTIFICATION WAS PROVIDED.

EACH PARTY TO THE ACTION HAS AN AFFIRMATIVE DUTY TO REASONABLY COOPERATE IN EXPEDITING THE ACTION. IF THE PLAINTIFF BREACHES THAT DUTY, THE COURT MAY SHORTEN THE 18 MONTH PERIOD AS IT DEEMS APPROPRIATE. IF THE DEFENDANT BREACHES THAT DUTY, THE COURT MAY EXTEND THE 18-MONTH PERIOD AS IT DEEMS APPROPRIATE.

IF THE COURT DECIDES THAT THE PATENT IS INVALID OR NOT INFRINGED BEFORE THE EXPIRATION OF THE 18-MONTH PERIOD (OR SUCH SHORTER OR LONGER PERIOD AS THE COURT DECIDES), THEN THE APPROVAL MAY BE MADE EFFECTIVE ON THE DATE OF THE COURT DECISION. IF THE COURT DECIDES THAT THE PATENT INVALID OR INFRINGED BEFORE THE EXPIRATION OF THE 18 MONTH PERIOD, THEN THE APPROVAL MAY BE MADE EFFECTIVE ON SUCH DATE AS THE COURT ORDERS. THE COMMITTEE WANTS TO EMPHASIZE THAT THE COURT MAY NOT ORDER THE PAPER NDA APPROVED. THESE ARE TIMES WHEN THE APPROVAL OF A PAPER NDA MAY BE MADE EFFECTIVE IF THE FDA HAS COMPLETED ITS REVIEW OF THE PAPER NDA.

NO ACTION FOR A DECLARATORY JUDGMENT REGARDING THE PATENT AT ISSUE MAY BE BROUGHT BEFORE THE EXPIRATION OF THE 45 DAY PERIOD COMMENCING WITH THE PROVISION OF NOTICE OF THE CERTIFICATION OF PATENT INVALIDITY OR NON-INFRINGEMENT. AFTER THE 45 DAY PERIOD, ANY SUIT FOR DECLARATORY JUDGMENT REGARDING THE PATENT AT ISSUE MUST BE BROUGHT IN THE JUDICIAL DISTRICT WHERE THE DEFENDANT HAS ITS PRINCIPAL PLACE OF BUSINESS OR A REGULAR AND ESTABLISHED PLACE OF BUSINESS.

TRANSITION RULE

SECTION 505(C)(3)(D)(I) PROVIDES THAT THE FDA MAY NOT MAKE EFFECTIVE THE APPROVAL OF A PAPER NDA FOR A DRUG WHICH CONTAINS AN ACTIVE INGREDIENT (INCLUDING ANY ESTER OR SALT OF THE ACTIVE INGREDIENT) WHICH WAS APPROVED FOR THE FIRST TIME

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IN AN NDA BETWEEN JANUARY 1, 1982 AND THE DATE OF ENACTMENT OF THIS BILL UNTIL 10 YEARS AFTER THE DATE OF APPROVAL OF THE NDA. FOR EXAMPLE, IF ACTIVE INGREDIENT X WAS APPROVED IN A DRUG FOR THE FIRST TIME IN 1983, THEN THE APPROVAL OF A PAPER NDA FOR A DRUG CONTAINING ACTIVE INGREDIENT X COULD NOT BE MADE EFFECTIVE UNTIL 1993.

UNPATENTABLE DRUGS

IF THE ACTIVE INGREDIENT (INCLUDING ANY ESTER OR SALT OF THE ACTIVE INGREDIENT) OF A DRUG IS APPROVED FOR THE FIRST TIME IN AN NDA AFTER ***35 **2668** THE ENACTMENT OF THIS BILL, THEN SECTION 505(C)(3)(D)(II) PROVIDES THAT THE FDA MAY NOT MAKE THE APPROVAL OF A PAPER NDA FOR A DRUG WHICH CONTAINS THAT ACTIVE INGREDIENT EFFECTIVE UNTIL FOUR YEARS AFTER THE APPROVAL OF THE NDA IF THE FOLLOWING CONDITIONS ARE MET.

THE HOLDER OF THE NDA MUST CERTIFY THAT NO PATENT HAS EVER BEEN ISSUED TO ANY PERSON FOR SUCH DRUG OR FOR A METHOD OF USING SUCH DRUG. FURTHER, THE HOLDER MUST CERTIFY THAT HE CANNOT RECEIVE A PATENT FOR SUCH DRUG OR FOR A METHOD USING SUCH DRUG FOR ANY KNOWN THERAPEUTIC PURPOSE.

IF THE FDA DETERMINES AT ANY TIME DURING THE FOUR YEAR PERIOD THAT AN ADEQUATE SUPPLY OF THE DRUG WILL NOT BE AVAILABLE, IT MAY MAKE THE APPROVAL OF A PAPER NDA EFFECTIVE BEFORE THE EXPIRATION OF THE FOUR YEAR PERIOD. THE FDA MAY ALSO MAKE THE APPROVAL OF A PAPER NDA FOR THE DRUG EFFECTIVE BEFORE THE FOUR YEAR PERIOD IF THE HOLDER OF THE NDA CONSENTS.

SECTION 104

SECTION 104 AMENDS SECTION 505 OF THE FFDCA TO ADD A NEW SUBSECTION (1). THIS NEW SUBSECTION PROVIDES THAT SAFETY AND EFFECTIVENESS INFORMATION THAT HAS BEEN SUBMITTED IN AN NDA AND WHICH HAS NOT BEEN PREVIOUSLY DISCLOSED TO THE PUBLIC SHALL BE MADE AVAILABLE TO THE PUBLIC UPON REQUEST UNDER THE FOLLOWING CIRCUMSTANCES UNLESS EXTRAORDINARY CIRCUMSTANCES ARE SHOWN.

FIRST, THE SAFETY AND EFFECTIVENESS INFORMATION AND DATA SHALL BE DISCLOSED UPON REQUEST IF THE NDA HAS BEEN ABANDONED. SECOND, SUCH INFORMATION AND DATA SHALL BE MADE AVAILABLE UPON REQUEST IF THE FDA HAS DETERMINED THAT THE NDA IF NOT APPROVABLE AND ALL LEGAL APPEALS HAVE BEEN EXHAUSTED. THIRD, THE DATA AND INFORMATION SHALL BE RELEASED UPON REQUEST IF THE APPROVAL OF THE NDA UNDER SECTION 505(C) OF THE FFDCA HAS BEEN WITHDRAWN AND ALL LEGAL APPEALS HAVE BEEN EXHAUSTED. FOURTH, SUCH INFORMATION AND DATA SHALL BE RELEASED UPON REQUEST IF THE FDA HAS DETERMINED THAT THE DRUG WHICH IS THE SUBJECT OF THE NDA IS NOT A NEW DRUG.

THESE CONDITIONS UNDER WHICH SUCH SAFETY AND EFFECTIVENESS DATA SHALL BE RELEASED UPON REQUEST, UNLESS EXTRAORDINARY CIRCUMSTANCES ARE SHOWN, ARE MERELY A RESTATEMENT OF THE CURRENT REGULATION. THE COMMITTEE INTENDS THAT ALL TERMS IN NEW SECTION 505(1) BE GIVEN THE SAME MEANING THAT THEY HAVE IN THE REGULATION. [FN18] IT IS NOT THE INTENT OF THE COMMITTEE TO ALTER THE RIGHTS OF THE PUBLIC UNDER THE FREEDOM OF INFORMATION ACT.

THE COMMITTEE DOES INTEND, HOWEVER, TO CLARIFY THE INTERPRETATION OF 21 C.F.R.

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314.14(F)(5). [FN19] IN THIS CIRCUMSTANCE, SAFETY AND EFFECTIVENESSDATA ***36 ****2669*** AND INFORMATION MAY BE RELEASED UPON THE EFFECTIVE DATE OF THE FIRST APPROVAL OF AN ANDA FOR SUCH DRUG UNDER NEW SUBSECTION (J) OF SECTION 505 OF THE FFDCA. FURTHER, THE INFORMATION AND DATA MAY BE RELEASED ON THE DATE UPON WHICH AN APPROVAL OF AN ANDA COULD BE MADE EFFECTIVE IF AN ANDA HAD BEEN SUBMITTED. THE COMMITTEE RECOGNIZES THAT AN ANDA MAY NOT BE SUBMITTED FOR ALL DRUGS THAT ARE ELIGIBLE FOR APPROVAL AS GENERICS. TO DEAL WITH THAT POSSIBILITY, THE COMMITTEE INTENDS TO MAKE AVAILABLE THIS DATA WHEN THE APPROVAL OF AN ANDA WOULD HAVE BECOME EFFECTIVE.

THE COMMITTEE DOES NOT INTEND THAT ANY SAFETY AND EFFECTIVENESS DATA AND INFORMATION BE RELEASED PURSUANT TO THIS SECTION DURING THE 30 DAY PERIOD AFTER ENACTMENT OF THIS BILL WHEN PATENT INFORMATION MUST BE SUBMITTED UNDER SECTION 505(B) OR (C). OTHERWISE, ANDA'S FILED DURING THAT PERIOD COULD BE APPROVED EFFECTIVE IMMEDIATELY, THUS ALLOWING FOR THE DISCLOSURE OF SAFETY AND EFFECTIVENESS INFORMATION AND DATA FOR THOSE DRUGS.

THE COMMITTEE ALSO DOES NOT INTEND THAT SAFETY AND EFFECTIVENESS DATA AND INFORMATION BE RELEASED UNDER THIS SECTION IF AN ANDA CHALLENGING THE VALIDITY OF A PATENT IS APPROVED BEFORE THERE HAS BEEN A COURT DECISION HOLDING THE PATENT INVALID AND IF THE NDA HOLDER BRINGS AN ACTION TO RESTRAIN THE DISCLOSURE.

FINALLY, EXCEPT AS PROVIDED IN THIS SECTION, THE COMMITTEE DOES NOT INTEND TO CHANGE OTHER REGULATIONS REGARDING FREEDOM OF INFORMATION ACT REQUESTS, TRADE SECRETS, AND CONFIDENTIALITY OF IND, NDA AND MASTER FILE SAFETY AND EFFECTIVENESS INFORMATION AND DATA.

SECTION 104 ALSO ADDS A NEW SUBSECTION (M) TO SECTION 505 OF THE FFDCA. THIS PROVISION CLARIFIES THAT ANY REFERENCE TO PATENT INFORMATION IN SECTION 505 APPLIES ONLY TO PATENTS ISSUED BY THE PATENT AND TRADEMARK OFFICE OF THE DEPARTMENT OF COMMERCE. IT DOES NOT INCLUDE ANY PATENTS ISSUED BY FOREIGN GOVERNMENTS.

SECTION 105

SECTION 105(A) OF THE BILL REQUIRES THE FDA TO PROMULGATE SUCH REGULATIONS AS ARE NECESSARY TO IMPLEMENT NEW SUBSECTION (J). THESE REGULATIONS MUST BE PROMULGATED IN ACCORDANCE WITH THE INFORMAL RULEMAKING REQUIREMENTS OF TITLE 5 OF THE U.S.C. AND NOT LATER THAN ONE YEAR AFTER ENACTMENT OF THIS BILL.

SECTION 105(B) OF THE BILL ESTABLISHES AN INTERIM PROCEDURE FOR APPROVING ANDA'S FOR POST-1962 DRUGS UNTIL THE FINAL IMPLEMENTING REGULATIONS ARE PROMULGATED. DURING THE PERIOD AFTER ENACTMENT OF THIS BILL AND UNTIL THE PROMULGATION OF REGULATIONS BY THE FDA, ANDA'S FOR LISTED POST-1962 DRUGS MAY BE SUBMITTED IN ACCORDANCE WITH THE CURRENT REGULATIONS APPLICABLE TO PRE-1962 PIONEER DRUGS.

TO THE EXTENT THAT THERE ARE INCONSISTENCIES BETWEEN THE CURRENT REGULATIONS AND THIS ACT, THE FDA SHALL FOLLOW THIS ACT. UNDER NO CIRCUMSTANCES MAY THE FDA APPROVE AN ANDA OR PAPER NDA UNDER THIS INTERIM PROCEDURE FOR A DRUG THAT IS ELIGIBLE FOR FOUR OR TEN YEARS OF MARKET EXCLUSIVITY EXCEPT IN ACCORDANCE WITH THOSE PROVISIONS.

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SECTION 106 OF THE BILL AMENDS SECTION 2201 OF TITLE 28 TO INSERT A CROSS REFERENCE TO EXPLAIN THAT A SUIT FOR DECLARATORY JUDGMENT REGARDING A PATENT MAY NOT BE BROUGHT UNDER CERTAIN CIRCUMSTANCES SET FORTH IN SECTION 505 OF THE FFDCA.

TITLE II-- PATENT TERM RESTORATION ACT

SECTION 201 OF THE BILL

SECTION 201 ADDS A NEW SECTION 156 TO TITLE 35 OF THE U.S.C. THE PATENT LAW. IT IS ENTITLED 'EXTENSION OF PATENT TERM.' THE NEW SECTION PROVIDES FOR THE EXTENSION OF THE NORMAL 17 YEAR TERM OF A PRODUCT, USE, OR PROCESS PATENT IF A PRODUCT WHICH IS THE SUBJECT OF THE PATENT IS REQUIRED BY FEDERAL LAW TO BE APPROVED BEFORE IT IS COMMERCIALLY MARKETED.

SECTION 156(A)

CONDITIONS FOR EXTENSION APPLICABLE TO ALL PATENTS

THE TERM OF A PATENT WHICH CLAIMS A PRODUCT, A METHOD OF USING A PRODUCT, OR A METHOD OF MANUFACTURING A PRODUCT SHALL BE EXTENDED ONE TIME FROM ITS ORIGINAL EXPIRATION DATE IF THE CONDITIONS DESCRIBED IN SECTION 156(A) ARE MET. THE TERM 'CLAIMS' WAS SELECTED BECAUSE IT IS THE TERM USED IN THE PATENT LAW TO DESCRIBE THE INVENTION WHICH THE PATENT OWNER OR ITS ASSIGNEE MAY PREVENT OTHERS FROM MAKING, USING OR SELLING DURING THE SEVENTEEN YEAR TERM OF THE PATENT. FOR INSTANCE, IN THE CASE OF A PRODUCT PATENT WHICH 'CLAIMS' A BROAD GENUS OF COMPOUNDS, THE PATENT OWNER COULD PREVENT OTHERS FROM MAKING, USING OR SELLING ANY COMPOUND WHICH IS A SPECIES OF THAT GENUS.

SIX OF THE EIGHT CONDITIONS DESCRIBED IN THE NUMBERED PARAGRAPHS UNDER SECTION 156(A) ARE APPLICABLE TO ALL PATENTS TO BE EXTENDED. THEY ARE FOUND IN PARAGRAPHS (1)-(3) AND (6)-(8).

PARAGRAPH (1) REQUIRES THE PATENT TO BE IN FORCE AT THE TIME AN APPLICATION FOR ITS EXTENSION IS SUBMITTED TO THE COMMISSIONER OF PATENTS AND TRADEMARKS. PARAGRAPH (2) ALLOWS EXTENSION ONLY IF THE TERM OF THE PATENT HAS NOT BEEN EXTENDED PREVIOUSLY. AND PARAGRAPH (3) REQUIRES THE APPLICATION FOR EXTENSION TO BE SUBMITTED BY THE OWNER OF RECORD OF THE PATENT, OR ITS AGENT, IN ACCORDANCE WITH THE REQUIREMENTS OF SECTION 156(D).

PARAGRAPHS (6) AND (7) DESCRIBE TWO CONDITIONS WHICH MUST BE MET BY THE PRODUCT WHICH IS CLAIMED IN THE PRODUCT PATENT TO BE EXTENDED, OR THE USE OR MANUFACTURE OF WHICH IS CLAIMED IN THE USE OR PROCESS PATENT TO BE EXTENDED. FIRST, THE PRODUCT MUST HAVE BEEN SUBJECTED TO A REGULATORY REVIEW PERIOD UNDER AN APPLICABLE FEDERAL LAW, AND APPROVED, BEFORE THE PRODUCT WAS ALLOWED TO BE COMMERCIALLY MARKETED. (THE PRODUCT WHICH CAN BE THE SUBJECT OF A PATENT EXTENSION IS HEREAFTER REFERRED TO AS THE 'APPROVED PRODUCT.') SECOND, WITH ONE EXCEPTION, THE APPROVED PRODUCT MUST HAVE BEEN APPROVED FOR COMMERCIAL MARKETING FOR THE FIRST TIME. THE EXCEPTION INVOLVES AN APPROVED PRODUCT MADE UNDER A PATENTED PROCESS WHICH PRIMARILY USES RECOMBINANT DNA TECHNOLOGY. SUCH AN APPROVED PRODUCT COULD

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HAVE RECEIVED ITS SECOND APPROVAL FOR COMMERCIAL ***38 **2671** MARKETING, BUT IT MUST BE THE FIRST TIME A PRODUCT MADE BY THE CLAIMED PROCESS HAS BEEN APPROVED.

THE COMMITTEE'S BILL REQUIRES EXTENSIONS TO BE BASED ON THE FIRST APPROVAL OF A PRODUCT BECAUSE THE ONLY EVIDENCE AVAILABLE TO CONGRESS SHOWING THAT PATENT TIME HAS BEEN LOST IS DATA ON SO-CALLED CLASS I, NEW CHEMICAL ENTITY DRUGS. THESE DRUGS HAD BEEN APPROVED BY THE FOOD AND DRUG ADMINISTRATION (FDA) FOR THE FIRST TIME. AN EXCEPTION WAS ALLOWED FOR PRODUCTS MADE THROUGH RECOMBINANT DNA BECAUSE THIS INNOVATIVE, NEW TECHNIQUE IS BEING EMPLOYED TO IMPROVE ALREADY APPROVED DRUGS.

PARAGRAPH (8) ADDRESSES THE CIRCUMSTANCES WHERE TWO DIFFERENT APPROVED PRODUCTS ARE THE SUBJECT OF THE SAME PATENT. AN EXTENSION WOULD BE GRANTED ONLY FOR THE FIRST APPROVED PRODUCT WHICH HAS BEEN THE SUBJECT OF A REGULATORY REVIEW PERIOD.

CONDITIONS OF EXTENSION APPLICABLE TO PRODUCT AND USE PATENTS

PARAGRAPH (4) OF SECTION 156(A) DESCRIBES CONDITIONS WHICH ARE APPLICABLE TO PRODUCT AND USE PATENTS ONLY.

PARAGRAPH (4)(A) PERMITS SUCH A PATENT TO BE EXTENDED IF TWO REQUIREMENTS ARE MET. THE FIRST IS THAT THE APPROVED PRODUCT IS NOT CLAIMED IN ANOTHER PRODUCT PATENT WHICH HAS BEEN EXTENDED OR WHICH AS AN EARLIER ISSUANCE DATE. THE SECOND IS THAT THE APPROVED PRODUCT AND THE USE FOR WHICH THE PRODUCT IS APPROVED ARE NOT IDENTICALLY DISCLOSED OR DESCRIBED IN ANOTHER PRODUCT OR USE PATENT WHICH HAS BEEN EXTENDED OR WHICH HAS AN EARLIER ISSUANCE DATE. THE PHRASE 'IDENTICALLY DISCLOSED OR DESCRIBED' IS INTENDED TO HAVE THE SAME MEANING WHICH IT HAS UNDER CURRENT PATENT LAW. [FN20]

THE POLICY WHICH THE COMMITTEE SEEKS TO IMPLEMENT IN PARAGRAPH (4)(A) IS, IN BRIEF, THAT THE FIRST PATENT (1) WHICH CLAIMS THE APPROVED PRODUCT, IN THE SENSE THAT THE APPROVED PRODUCT WOULD INFRINGE A CLAIM OF THAT PATENT, OR (2) WHICH FULLY DISCLOSES THAT PRODUCT AND ITS APPROVED USE, IS THE PATENT WHICH SHOULD BE REWARDED WITH AN EXTENSION. FOR EXAMPLE, IF THE APPROVED PRODUCT IS THE SUBJECT OF SEVERAL PATENTS AS A RESULT OF FILING CONTINUATION, CONTINUATION-IN-PART, DIVISIONAL OR OTHERWISE RELATED PATENT APPLICATIONS, EACH OF WHICH DISCLOSES THE APPROVED PRODUCT AND ITS APPROVED USE, THEN ONLY THE EARLIEST ISSUED PATENT IS ELIGIBLE FOR AN EXTENSION.

PARAGRAPH (4)(B) IS AN EXCEPTION TO THE RULE IN PARAGRAPH (4)(A) FOR CERTAIN PRODUCT PATENTS. IF TWO CONDITIONS ARE MET, A PRODUCT PATENT CAN BE EXTENDED EVEN THOUGH THE APPROVED PRODUCT IS ALSO CLAIMED IN ANOTHER PRODUCT PATENT WHICH HAS BEEN EXTENDED OR WHICH HAS AN EARLIER ISSUANCE DATE. FIRST, THE PRODUCT PATENT WHICH WAS ISSUED EARLIER OR PREVIOUSLY EXTENDED CANNOT IDENTICALLY DISCLOSE OR DESCRIBE THE APPROVED PRODUCT. SECOND, THE HOLDER OF EACH OF THE TWO PRODUCT PATENTS MUST NEVER HAVE BEEN AND MUST NEVER BECOME THE HOLDER OF THE OTHER PATENT. IN THIS PARAGRAPH, THE TERM 'HOLDER' IS ANY PERSON WHO OWNS THE PATENT OR IS AN EXCLUSIVE LICENSEE OF THE OWNER. THIS EXCEPTION WAS INCLUDED TO PREVENT AN EARLIER ISSUED PATENT WHICH CLAIMS A BROAD GENUS OF COMPOUNDS FROM BLOCKING THE POSSIBLE EXTENSION OF A LATER ISSUED PATENT CLAIMING A ***39 **2672** SPECIFIC MEMBER OF THAT GENUS WHERE NEITHER PATENT HOLDER HAD A CHOICE AS TO WHICH PATENT TO EXTEND.

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CONDITIONS OF EXTENSION APPLICABLE TO PROCESS PATENTS

PARAGRAPH (5) OF SECTION 156(A) DESCRIBES CONDITIONS WHICH ARE APPLICABLE TO PROCESS PATENTS ONLY.

PARAGRAPH (5)(A) PERMITS A PROCESS PATENT, WHICH DOES NOT PRIMARILY UTILIZE RECOMBINANT DNA IN THE MANUFACTURE OF THE APPROVED PRODUCT, TO BE EXTENDED IF TWO CONDITIONS ARE MET. FIRST, THERE CAN NOT BE ANY ISSUED PRODUCT PATENT WHICH CLAIMS THE APPROVED PRODUCT OR ANY ISSUED USE PATENT WHICH CLAIMS A METHOD OF USING THE APPROVED PRODUCT FOR ANY KNOWN THERAPEUTIC USE. AND, SECOND, THERE CAN NOT BE AN EARLIER ISSUED PROCESS PATENT, WHICH DOES NOT PRIMARILY UTILIZE RECOMBINANT DNA AND WHICH CLAIMS A METHOD OF MANUFACTURING THE APPROVED PRODUCT.

PARAGRAPH (5)(B) PERMITS A PROCESS PATENT, WHICH PRIMARILY UTILIZES RECOMBINANT DNA IN THE MANUFACTURE OF THE APPROVED PRODUCT, TO BE EXTENDED IF SEVERAL CONDITIONS ARE MET. FIRST, THE HOLDER OF THE PROCESS PATENT CAN NOT HOLD A PRODUCT PATENT CLAIMING THE APPROVED PRODUCT OR A USE PATENT CLAIMING A METHOD OF USING THE APPROVED PRODUCT. SECOND, THERE CAN NOT BE AN OWNERSHIP OR CONTROL INTEREST, EITHER DIRECTLY OR INDIRECTLY, BETWEEN THE HOLDER OF THE PROCESS PATENT AND THE HOLDER OF ANY PRODUCT PATENT CLAIMING THE APPROVED PRODUCT OR THE HOLDER OF ANY USE PATENT CLAIMING A METHOD OF USING THE APPROVED PRODUCT. THIRD, THERE CAN NOT BE ANY EARLIER ISSUED PROCESS PATENT WHICH CLAIMS A METHOD OF MANUFACTURING THE APPROVED PRODUCT BY PRIMARILY UTILIZING RECOMBINANT DNA.

THE COMMITTEE'S BILL ESTABLISHES SEPARATE RULES FOR PROCESS PATENTS WHICH DO NOT USE RECOMBINANT DNA BECAUSE THE DISCOVERY OF SUCH A NEW PROCESS FOR MAKING AN EXISTING PRODUCT DOES NOT WARRANT THE SAME REWARD OF PATENT EXTENSION AS DOES THE DISCOVERY OF A NEW PRODUCT. AN EXTENSION FOR THE PROCESS PATENT IS APPROPRIATE ONLY WHEN THERE ARE NO PRODUCT OR USE PATENTS. ON THE OTHER HAND, WHEN RECOMBINANT DNA TECHNOLOGY IS THE ESSENTIAL AND PREDOMINANT TECHNIQUE USED IN MAKING AN IMPROVED VERSION OF AN EXISTING PRODUCT, THE COMMITTEE BELIEVES THAT THIS NEW AND IMPORTANT INNOVATION SHOULD BE REWARDED.

SECTION 156(B)

RIGHTS TO BE EXTENDED

EXCEPT FOR THE LIMITATIONS DESCRIBED BELOW WITH RESPECT TO THE SCOPE OF THE PATENT CLAIMS, ALL PROVISIONS OF THE PATENT LAW APPLY TO THE PATENT DURING THE PERIOD OF EXTENSION. THE LIMITATIONS ARE AS FOLLOWS: (1) WHEN A PRODUCT PATENT CLAIMING THE APPROVED PRODUCT IS EXTENDED, THE HOLDER'S RIGHTS ARE LIMITED TO ANY USE OF THE APPROVED PRODUCT WHICH WAS APPROVED BEFORE THE EXPIRATION OF THE EXTENDED TERM OF THE PATENT UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED.

(2) WHEN A USE PATENT CLAIMING A METHOD OF USING THE APPROVED PRODUCT IS EXTENDED, THE HOLDER'S RIGHTS ARE LIMITED TO ANY USE OF THE APPROVED PRODUCT WHICH: (1) IS CLAIMED IN THE USE PATENT, AND (B) WAS APPROVED BEFORE THE EXPIRATION OF THE EXTENDED TERM OF THE ***40 ****2673** PATENT UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED.

(3) WHEN A PROCESS PATENT CLAIMING A METHOD OF MANUFACTURING THE APPROVED

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PRODUCT IS EXTENDED, THE HOLDER'S RIGHTS ARE LIMITED TO THE METHOD OF MANUFACTURING WHICH: (A) IS CLAIMED IN THE PROCESS PATENT, AND (B) IS USED TO MAKE THE APPROVED PRODUCT.

SECTION 156(C)

PERIOD OF EXTENSION

SECTION 156(C) SPECIFIES THE RULES BY WHICH THE LENGTH OF THE PERIOD OF EXTENSION IS DETERMINED. THE CALCULATION MADE UNDER THESE RULES IS FURTHER LIMITED BY THE REQUIREMENTS OF SECTION 156(G)(4).

UNDER SECTION 156(C), THE LENGTH OF THE EXTENSION IS BASED ON THE LENGTH OF THE REGULATORY REVIEW PERIOD IN WHICH THE APPROVED PRODUCT WAS APPROVED. THE DEFINITION OF THE VARIOUS REGULATORY REVIEW PERIODS IS IN SECTIONS 156(G) (1)-(3). ALL REGULATORY REVIEW PERIODS ARE DIVIDED INTO A TESTING PHASE AND AN AGENCY APPROVAL PHASE.

THE REGULATORY REVIEW PERIOD WHICH OCCURS AFTER THE PATENT TO BE EXTENDED WAS ISSUED IS ELIGIBLE TO BE COUNTED TOWARDS EXTENSION IN ACCORDANCE WITH THE FOLLOWING CALCULATION. FIRST, EACH PHASE OF THE REGULATORY REVIEW PERIOD IS REDUCED BY ANY TIME THAT THE APPLICANT FOR EXTENSION DID NOT ACT WITH DUE DILIGENCE DURING THAT PHASE. (THE DETERMINATION OF LACK OF DUE DILIGENCE IS MADE UNDER SECTION 156(D).) SECOND, AFTER ANY SUCH REDUCTION, ONE-HALF OF THE TIME REMAINING IN THE TESTING PHASE WOULD BE ADDED TO THE TIME REMAINING IN THE APPROVAL PHASE TO COMPRISE THE TOTAL PERIOD ELIGIBLE FOR EXTENSION. THIRD, ALL OF THE ELIGIBLE PERIOD CAN BE COUNTED UNLESS TO DO SO WOULD RESULT IN A TOTAL REMAINING PATENT TERM OF MORE THAN FOURTEEN YEARS. FOR EXAMPLE, IF AN APPROVED DRUG PRODUCT WHICH IS ELIGIBLE FOR FIVE YEARS OF EXTENSION HAD TEN YEARS OF ORIGINAL PATENT TERM LEFT AT THE END OF ITS REGULATORY REVIEW PERIOD, THEN ONLY FOUR OF THE FIVE YEARS COULD BE COUNTED TOWARDS EXTENSION.

THE ADDITIONAL LIMITATION ON THE PERIOD OF EXTENSION IS FOUND IN SECTION 156(G)(4). THAT SECTION PROVIDES DIFFERENT MAXIMUM PERIODS OF EXTENSION DEPENDING ON WHETHER THE APPROVED PRODUCT WAS DEVELOPED BEFORE OR AFTER THE DATE OF ENACTMENT.

UNDER THAT SECTION, THE TOTAL PERIOD OF REGULATORY REVIEW WHICH CAN BE COUNTED TOWARDS EXTENSION WOULD NOT EXCEED FIVE YEARS WHEN: (1) THE PATENT TO BE EXTENDED WAS ISSUED AFTER THE DATE OF ENACTMENT OF THIS BILL; OR (2) THE PATENT WAS ISSUED BEFORE THE DATE OF ENACTMENT, BUT THE APPROVED PRODUCT'S REGULATORY REVIEW PERIOD HAD NOT BEGUN ON THE DATE OF ENACTMENT. THE TOTAL PERIOD OF ELIGIBLE REGULATORY REVIEW WOULD NOT EXCEED TWO YEARS WHEN: (1) THE PATENT TO BE EXTENDED WAS ISSUED BEFORE THE DATE OF ENACTMENT; AND (2) THE APPROVED PRODUCT'S REGULATORY REVIEW PERIOD HAD BEGUN BEFORE THE DATE OF ENACTMENT BUT THE PRODUCT HAD NOT BEEN APPROVED BY THAT DATE. IF ANY ACTION WAS TAKEN BEFORE THE DATE OF ENACTMENT WHICH INITIATED THE TESTING PHASE OF THE REGULATORY REVIEW PERIOD, THEN THE APPLICANT WOULD NOT BE ELIGIBLE FOR THE FIVE YEAR RULE BY DISCONTINUING ACTIVITY AND THEN INITIATING A NEW REGULATORY REVIEW PERIOD AFTER THE DATE OF ENACTMENT.

***41 **2674** THE COMMITTEE ESTABLISHED DIFFERENT MAXIMUM PERIODS OF EXTENSION TO PROVIDE GREATER INCENTIVE FOR FUTURE INNOVATIONS. BY EXTENDING PATENTS FOR UP TO

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FIVE YEARS FOR PRODUCTS DEVELOPED IN THE FUTURE, AND BY PROVIDING FOR UP TO FOURTEEN YEARS OF MARKET EXCLUSIVITY, THE COMMITTEE EXPECTS THAT RESEARCH INTENSIVE COMPANIES WILL HAVE THE NECESSARY INCENTIVE TO INCREASE THEIR RESEARCH AND DEVELOPMENT ACTIVITIES.

SECTION 156(D)

APPLICATION FOR EXTENSION

TO OBTAIN AN EXTENSION, THE PATENT OWNER OR ITS AGENT WOULD SUBMIT AN APPLICATION TO THE COMMISSIONER OF PATENTS AND TRADEMARKS WITHIN 60 DAYS OF APPROVAL OF THE APPROVED PRODUCT. THE APPLICATION WOULD CONTAIN THE INFORMATION DESCRIBED IN SUBPARAGRAPHS (A)-(G) OF SECTION 156(D)(1). THE APPLICANT WOULD BE SUBJECT TO ANY DISCLOSURE REQUIREMENTS PRESCRIBED BY THE COMMISSIONER. THE COMMITTEE EXPECTS THAT THOSE REQUIREMENTS WOULD SUBJECT THE APPLICANT TO AT LEAST THE SAME DUTY OF DISCLOSURE, AND THE PENALTIES AND LOSS OF RIGHTS FOR VIOLATION OF THE DUTY OF DISCLOSURE, WHICH GOVERNS ALL PATENT APPLICATION PROCEEDINGS BEFORE THE PATENTS AND TRADEMARKS OFFICE.

WITHIN 60 DAYS OF THE SUBMISSION OF AN APPLICATION, THE COMMISSIONER WOULD NOTIFY THE SECRETARY OF HEALTH AND HUMAN SERVICES, OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO REVIEW THE DATES CONTAINED IN THE APPLICATION FOR THE REGULATORY REVIEW PERIOD. WITHIN 30 DAYS, THE APPROPRIATE SECRETARY WOULD MAKE A DETERMINATION AS TO THOSE DATES, NOTIFY THE COMMISSIONER OF THEM, AND PUBLISH THEM IN THE FEDERAL REGISTER.

DETERMINATION OF DUE DILIGENCE (SECTION 156(D)(2)(B))

THE COMMITTEE'S BILL PROVIDES A DEFINITION OF DUE DILIGENCE AT SECTION 156(D)(3). IT IS 'THAT DEGREE OF ATTENTION, CONTINUOUS DIRECTED EFFORT, AND TIMELINESS AS MAY REASONABLY BE EXPECTED FROM, AND ARE ORDINARILY EXERCISED BY, A PERSON DURING A REGULATORY REVIEW PERIOD.'

A PETITION MAY BE SUBMITTED BY ANY INTERESTED PERSON TO THE APPROPRIATE SECRETARY REQUESTING A DETERMINATION OF WHETHER THE APPLICANT FOR EXTENSION ACTED WITH DUE DILIGENCE DURING THE REGULATORY REVIEW PERIOD OF THE APPROVED PRODUCT. THE PETITION MUST BE SUBMITTED WITHIN 180 DAYS OF THE PUBLICATION BY THE SECRETARY OF A DETERMINATION OF THE REGULATORY REVIEW PERIOD AND MUST STATE CLAIM THAT THE APPLICANT DID NOT ACT WITH DUE DILIGENCE DURING SOME PART OF THE REGULATORY REVIEW PERIOD. IF THE SECRETARY CONCLUDES FROM THE INFORMATION IN THE PETITION THAT THERE IS REASON TO BELIEVE THAT THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AT SOME POINT IN THE REGULATORY REVIEW PERIOD, THEN THE SECRETARY WOULD MAKE, WITHIN 90 DAYS OF THE RECEIPT OF THE PETITION AND IN ACCORDANCE WITH REGULATIONS, A DETERMINATION OF WHETHER THE APPLICANT ACTED WITH DUE DILIGENCE. THE SECRETARY OF HHS IS PROHIBITED FROM DELEGATING THE AUTHORITY TO MAKE THE DETERMINATION TO ANY OFFICE BELOW THAT OF THE COMMISSIONER OF FDA.

WHILE THE BILL PLACES THE BURDEN ON THE PETITIONER TO MAKE THE NECESSARY SHOWING, THE COMMITTEE RECOGNIZES THAT THE INFORMATION ***42 **2675** NEEDED TO MAKE A FINAL DETERMINATION OF DUE DILIGENCE IS NOT AVAILABLE TO THE PETITIONER. TO MEET

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THIS BURDEN OF PROOF, THE PETITIONER NEED NOT SHOW CONCLUSIVELY THAT THERE WAS A LACK OF DUE DILIGENCE. INSTEAD, THE PETITIONER NEED ONLY ALLEGE SUFFICIENT FACTS TO MERIT AN INVESTIGATION BY THE SECRETARY. FOR EXAMPLE, IT WOULD BE SUFFICIENT FOR THE PETITIONER TO DEMONSTRATE THAT HUMAN CLINICAL TRIALS DID NOT BEGIN FOR AN UNREASONABLY LONG PERIOD OF TIME AFTER THE FDA GRANTED PERMISSION TO BEGIN THOSE TRIALS OR THAT THE TRIALS TOOK AN UNREASONABLY LONG PERIOD OF TIME. IN THOSE EVENTS, THE SECRETARY WOULD DETERMINE WHETHER THE DELAY WAS CAUSED BY A LACK OF DUE DILIGENCE ON THE PART OF THE APPLICANT.

AFTER MAKING THE DETERMINATION, THE SECRETARY WOULD NOTIFY THE COMMISSIONER OF PATENTS AND TRADEMARKS AND PUBLISH IT IN THE FEDERAL REGISTER. ANY INTERESTED PERSON COULD REQUEST AN INFORMAL HEARING WITHIN 60 DAYS OF PUBLICATION OF THE DETERMINATION. IF A TIMELY REQUEST IS MADE, THE SECRETARY MUST HOLD SUCH A HEARING WITHIN 30 DAYS, GIVE NOTICE OF THE HEARING TO THE PATENT OWNER AND ANY INTERESTED PERSON, AND PROVIDE SUCH PERSONS WITH AN OPPORTUNITY TO PARTICIPATE. WITHIN 30 DAYS OF THE HEARING, THE SECRETARY MUST AFFIRM OR REVISE THE DETERMINATION, NOTIFY THE COMMISSIONER OF PATENTS, AND PUBLISH IT IN THE FEDERAL REGISTER.

THE COMMITTEE ESTABLISHED A SYSTEM FOR REVIEW OF DUE DILIGENCE THAT REQUIRES THE MINIMAL AMOUNT OF FEDERAL AGENCY PERSONNEL TIME. THE GOAL OF THE SYSTEM IS TO ASSURE THAT OBVIOUS DELAYS DURING REGULATORY REVIEW, SUCH AS A PROLONGED PERIOD WHEN HUMAN CLINICAL TRIALS ON A DRUG PRODUCT ARE NOT BEING CONDUCTED, ARE NOT COUNTED TOWARDS PATENT EXTENSION. THE SYSTEM IS NOT INTENDED TO CAUSE A REVIEW OF EVERY ACTION, BUT TO IDENTIFY SIGNIFICANT PERIODS OF TIME WHEN THE LOSS OF PATENT TERM RESULTED SOLELY FROM THE APPLICANT'S FAILURE TO PURSUE APPROVAL. DELAYS CAUSED BY THE TEMPORARY UNAVAILABILITY OF NECESSARY TESTING FACILITIES, OR A SCIENTIFIC DISPUTE INVOLVING TESTS REQUIRED FOR APPROVAL OR THE INTERPRETATION OF THOSE TESTS, ARE EXAMPLES OF DELAYS WHICH CAN REASONABLY BE EXPECTED TO OCCUR AND WOULD NOT BE A BASIS FOR FINDING A LACK OF DUE DILIGENCE.

SECTION 156(E)

DETERMINATION ON PATENT EXTENSION OF THE COMMISSIONER OF PATENTS AND TRADEMARKS

THE COMMISSIONER WOULD MAKE THE FINAL DETERMINATION THAT A PATENT IS ELIGIBLE FOR EXTENSION UNDER SECTION 156(A), THAT THE REQUIREMENTS OF SECTION 156(D) HAVE BEEN MET, AND THAT THE PERIOD OF EXTENSION WILL BE THE PERIOD PRESCRIBED IN SECTION 156(C). ONCE THESE FINDINGS ARE MADE, THE COMMISSIONER WOULD BE REQUIRED TO ISSUE A CERTIFICATE OF EXTENSION TO THE APPLICANT. THE CERTIFICATE WOULD BE RECORDED IN THE OFFICIAL FILE OF THE PATENT AND BE CONSIDERED A PART OF THE ORIGINAL PATENT.

THE COMMISSIONER'S DECISION REGARDING A PATENT'S ELIGIBILITY FOR EXTENSION UNDER THE RULES OF SECTION 156(A) MAY BE BASED SOLELY ON THE INFORMATION CONTAINED IN THE APPLICATION. THE BURDEN IS ON THE APPLICANT TO SHOW THAT ALL PATENTS WHICH ARE RELEVANT TO THE ELIGIBILITY DETERMINATION HAVE BEEN CONSIDERED AND DO NOT PREVENT THE REQUESTED EXTENSION.

***43 **2676** WHILE THE COMMISSIONER WOULD BE RESPONSIBLE FOR EVALUATING THE APPLICANT'S DETERMINATION REGARDING THE PATENTS LISTED IN THE APPLICATION, THE

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COMMITTEE EXPECTS THAT MOST REVIEWS WOULD BE MINISTERIAL IN NATURE. SINCE THE APPLICANT IS UNDER A DUTY TO DISCLOSE ALL RELEVANT INFORMATION (SEE SECTION 156(D)(4)), THE APPLICATION SHOULD BE SO WELL DOCUMENTED THAT A SUBSTANTIVE REVIEW BY THE COMMISSIONER WOULD USUALLY NOT BE NECESSARY.

EXPIRATION OF A PATENT PENDING EXTENSION (SECTION 156(E)(2))

IT IS POSSIBLE THAT THE ORIGINAL TERM OF THE PATENT FOR WHICH EXTENSION IS SOUGHT COULD EXPIRE BEFORE A FINAL DECISION BY THE COMMISSIONER TO ISSUE A CERTIFICATE OF EXTENSION. THIS MIGHT OCCUR, FOR INSTANCE, BECAUSE THE DETERMINATION OF DUE DILIGENCE BY THE SECRETARY OF HHS OR AGRICULTURE HAS NOT BEEN COMPLETED.

IN SUCH CIRCUMSTANCES, THE COMMISSIONER IS REQUIRED TO DETERMINE WHETHER THE PATENT IS ELIGIBLE FOR EXTENSION UNDER SECTION 156(A), AND IF IT IS, TO ISSUE A CERTIFICATE OF EXTENSION FOR A PERIOD OF UP TO ONE YEAR. THE LENGTH OF THIS INTERIM EXTENSION IS DISCRETIONARY WITH THE COMMISSIONER, BUT IS INTENDED TO PROVIDE TIME FOR THE COMPLETION OF ANY OUTSTANDING REQUIREMENTS. IF THE COMMISSIONER DETERMINED THAT SUBSEQUENT INTERIM EXTENSIONS WERE NECESSARY, AND CONSISTENT WITH THE OBJECTIVES OF SECTION 156(E)(2), THEY COULD BE GRANTED AS WELL. IN NO EVENT COULD THESE INTERIM EXTENSIONS BE LONGER THAN THE MAXIMUM PERIOD OF EXTENSION TO WHICH THE APPLICANT IS THOUGHT TO BE ELIGIBLE.

SECTION 156(F)

DEFINITIONS

THE TERM 'PRODUCT' IS DEFINED IN SUBSECTION (F)(1) TO INCLUDE DRUG PRODUCTS AND MEDICAL DEVICES, FOOD ADDITIVES AND COLOR ADDITIVES SUBJECT TO REGULATION UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

THE TERM 'DRUG PRODUCT' IS DEFINED IN SUBSECTION (F)(2) TO MEAN THE ACTIVE INGREDIENT OF A NEW DRUG, ANTIBIOTIC DRUG, NEW ANIMAL DRUG, OR HUMAN OR VETERINARY BIOLOGICAL PRODUCT (AS THOSE TERMS ARE USED IN THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, THE PUBLIC HEALTH SERVICE ACT AND THE VIRUS-SERUM-TOXIN ACT), INCLUDING ANY SALT OR ESTER OF THE ACTIVE INGREDIENT, AS A SINGLE ENTITY OR IN COMBINATION WITH ANOTHER ACTIVE INGREDIENT. THE HUMAN DRUGS INCLUDED IN THIS DEFINITION ARE BOTH PRESCRIPTION AND OVER-THE-COUNTER DRUGS.

THE TERM 'MAJOR HEALTH OR ENVIRONMENTAL EFFECTS TEST' IS DEFINED IN SUBSECTION (F)(3) TO MEAN A TEST WHICH IS REASONABLY RELATED TO THE EVALUATION OF THE HEALTH OR ENVIRONMENTAL EFFECTS OF A PRODUCT, WHICH REQUIRES AT LEAST SIX MONTHS TO CONDUCT, AND THE DATA FROM WHICH IS SUBMITTED TO RECEIVE PERMISSION FOR COMMERCIAL MARKETING OR USE. PERIODS OF ANALYSIS OR EVALUATION OF TEST RESULTS ARE NOT TO BE INCLUDED IN DETERMINING IF THE CONDUCT OF A TEST REQUIRED AT LEAST SIX MONTHS.

THE TERM 'INFORMAL HEARING' IS DEFINED IN SUBSECTION (F)(5) TO HAVE THE SAME MEANING AS 'PRESCRIBED FOR SUCH TERM BY SECTION 201(Y) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.'

THE TERM 'PATENT' IS DEFINED IN SUBSECTION (F)(6) TO MEAN 'A PATENT ISSUED BY THE UNITED STATES PATENT AND TRADEMARK OFFICE.

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***44 **2677** SECTION 156(G)

DEFINITION OF REGULATORY REVIEW PERIOD

THE 'REGULATORY REVIEW PERIOD' DIFFERS FOR EACH PRODUCT THAT CAN BE THE SUBJECT OF PATENT EXTENSION, BUT IN ALL CASES IT IS CONSIDERED TO HAVE A TESTING PHASE AND AN AGENCY APPROVAL PHASE.

IN SECTIONS 156(G)(1)-(3) OF THE TERM 'INITIALLY SUBMITTED' IS USED TO DESCRIBE THE POINT IN TIME WHEN THE TESTING PHASE IS CONSIDERED TO BE COMPLETED AND THE AGENCY APPROVAL PHASE TO HAVE BEGUN. THIS TERM IS USED INSTEAD OF THE TERM 'FILED,' BECAUSE AN APPLICATION IS OFTEN NOT CONSIDERED TO BE FILED, EVEN THOUGH AGENCY REVIEW HAS BEGUN, UNTIL THE AGENCY HAS DETERMINED THAT NO OTHER INFORMATION IS NEEDED AND A DECISION ON THE APPLICATION CAN BE MADE. FOR PURPOSES OF DETERMINING THE REGULATORY REVIEW PERIOD AND ITS COMPONENT PERIODS, AN APPLICATION FOR AGENCY REVIEW IS CONSIDERED TO BE 'INITIALLY SUBMITTED' IF THE APPLICANT HAS MADE A DELIBERATE EFFORT TO SUBMIT AN APPLICATION CONTAINING ALL INFORMATION NECESSARY FOR AGENCY REVIEW TO BEGIN. THE COMMITTEE RECOGNIZES THAT THE AGENCY RECEIVING THE APPLICATION MIGHT DECIDE IT NEEDS ADDITIONAL INFORMATION OR OTHER CHANGES IN THE APPLICATION. AS LONG AS THE APPLICATION WAS COMPLETE ENOUGH SO THAT AGENCY ACTION COULD BE COMMENCED, IT WOULD BE CONSIDERED TO BE 'INITIALLY SUBMITTED'.

DRUG PRODUCTS (SECTION 156(G)(1)

THE REGULATORY REVIEW PERIOD FOR DRUG PRODUCTS IS THE SUM OF THE PERIODS: (1) BEGINNING WHEN AN EXEMPTION UNDER 505(I), 507(D), OR 512(J) WAS GRANTED OR AUTHORITY TO PREPARE AN EXPERIMENTAL DRUG PRODUCT UNDER THE VIRUS-SERUM-TOXIN ACT WAS GRANTED AND ENDING WHEN WITH THE INITIAL SUBMISSION OF AN APPLICATION FOR APPROVAL UNDER SECTION 351 OF THE PUBLIC HEALTH SERVICE ACT, 505, 507, 512 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, OR THE VIRUS-SERUM-TOXIN ACT; AND (2) BEGINNING WHEN AN APPLICATION FOR APPROVAL WAS INITIALLY SUBMITTED UNDER SECTION 351 OF THE PHS, 505, 507, 512 OF THE FFDCA OR THE VIRUS-SERUM-TOXIN ACT AND ENDING WHEN THE APPLICATION WAS APPROVED.

FOOD AND COLOR ADDITIVES (SECTION 156(G)(2))

THE REGULATORY REVIEW PERIOD FOR FOOD AND COLOR ADDITIVES IS THE SUM OF THE PERIODS: (1) BEGINNING WHEN A MAJOR HEALTH OR ENVIRONMENTAL EFFECTS TEST FOR A FOOD OR COLOR ADDITIVE WAS INITIATED AND ENDING WHEN A PETITION REQUESTING THE ISSUANCE OF A REGULATION FOR USE OF THE ADDITIVE WAS INITIALLY SUBMITTED; AND (2) BEGINNING WHEN A PETITION FOR THE ISSUANCE OF A REGULATION WAS INITIALLY SUBMITTED AND ENDING WHEN THE REGULATION BECAME EFFECTIVE.

IF PERMISSION FOR COMMERCIAL MARKETING WAS DELAYED BECAUSE OBJECTIONS WERE FILED TO THE REGULATION, OR IF SUCH PERMISSION WAS INITIALLY GRANTED AND LATER REVOKED BEFORE ACTUAL MARKETING BEGAN BECAUSE OBJECTIONS WERE FILED TO THE REGULATION, THEN THE PERIOD DESCRIBED IN (2) ABOVE WOULD END WHEN THE OBJECTIONS WERE RESOLVED AND COMMERCIAL MARKETING WAS PERMITTED.

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MEDICAL DEVICES (SECTION 156(G)(3))

THE REGULATORY REVIEW PERIOD FOR MEDICAL DEVICES IS THE SUM OF THE PERIODS: (1) BEGINNING WHEN HUMAN CLINICAL INVESTIGATIONS ARE ***45 **2678** COMMENCED AND ENDING WHEN AN APPLICATION FOR APPROVAL WAS INITIALLY SUBMITTED; AND (2) BEGINNING WHEN AN APPLICATION FOR APPROVAL WAS INITIALLY SUBMITTED AND ENDING WHEN THE APPLICATION WAS APPROVED, OR BEGINNING WHEN A NOTICE OF COMPLETION OF A PRODUCT DEVELOPMENT PROTOCOL WAS INITIALLY SUBMITTED AND ENDING WHEN THE PROTOCOL WAS DECLARED COMPLETED.

LIMITATIONS ON THE REGULATORY REVIEW PERIOD (SECTION 156(G)(4))

A DISCUSSION OF THIS SECTION IS CONTAINED IN THE EARLIER SECTION 156(C) ENTITLED 'PERIOD OF EXTENSION'.

SECTION 156(H)

FEES FOR APPLICATIONS

THE COMMISSIONER OF PATENTS AND TRADEMARKS IS AUTHORIZED TO ESTABLISH SUCH FEES AS HE DETERMINES APPROPRIATE TO COVER THE ENTIRE COST OF THE PATENTS AND TRADEMARKS OFFICE OF RECEIVING AND ACTING UPON APPLICATIONS FOR PATENT EXTENSIONS.

SECTION 202 OF THE BILL

SECTION 202 CREATES A NEW SECTION 271(E) IN TITLE 35 OF THE U.S.C. THE PATENT LAW.

PATENT INFRINGEMENT (SECTION 271(E))

SECTION 271(E)(1) PROVIDES THAT IT SHALL NOT BE AN ACT OF INFRINGEMENT TO MAKE, USE, OR SELL A PATENTED INVENTION SOLELY FOR USES REASONABLY RELATED TO THE DEVELOPMENT AND SUBMISSION OF INFORMATION UNDER A FEDERAL LAW WHICH REGULATES THE APPROVAL OF DRUGS. THIS SECTION DOES NOT PERMIT THE COMMERCIAL SALE OF A PATENTED DRUG BY THE PARTY USING THE DRUG TO DEVELOP SUCH INFORMATION, BUT IT DOES PERMIT THE COMMERCIAL SALE OF RESEARCH QUANTITIES OF ACTIVE INGREDIENTS TO SUCH PARTY. THE INFORMATION WHICH CAN BE DEVELOPED UNDER THIS PROVISION IS THE TYPE WHICH IS REQUIRED TO OBTAIN APPROVAL OF THE DRUG. A PARTY WHICH DEVELOPS SUCH INFORMATION, BUT DECIDES NOT TO SUBMIT AN APPLICATION FOR APPROVAL, IS PROTECTED AS LONG AS THE DEVELOPMENT WAS DONE TO DETERMINE WHETHER OR NOT AN APPLICATION FOR APPROVAL WOULD BE SOUGHT.

SECTION 271(E)(2) PROVIDES THAT IT SHALL BE AN ACT OF PATENT INFRINGEMENT TO SUBMIT AN ANDA FOR A DRUG (1) WHICH IS CLAIMED IN A VALID PRODUCT PATENT, OR (2) A USE OF WHICH IS CLAIMED IN A VALID USE PATENT, IF THE PURPOSE OF SUBMITTING THE ANDA IS TO GET APPROVAL OF THE ANDA WITH AN EFFECTIVE DATE PRIOR TO THE EXPIRATION OF SUCH PATENTS.

THE PURPOSE OF SECTIONS 271(E)(1) AND (2) IS TO ESTABLISH THAT EXPERIMENTATION

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WITH A PATENTED DRUG PRODUCT, WHEN THE PURPOSE IS TO PREPARE FOR COMMERCIAL ACTIVITY WHICH WILL BEGIN AFTER A VALID PATENT EXPIRES, IS NOT A PATENT INFRINGEMENT. SINCE THE COMMITTEE'S SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT BEGAN CONSIDERATION OF THIS BILL, THE COURT OF APPEALS FOR THE FEDERAL CIRCUIT HELD THAT THIS TYPE OF EXPERIMENTATION IS INFRINGEMENT.

IN ROCHE PRODUCTS, INC. V. BOLAR PHARMACEUTICAL CO., INC.-- F.2D-- (FED. CIR., APRIL 23, 1984), THE COURT OF APPEALS FOR THE FEDERAL CIRCUIT HELD THAT THE EXPERIMENTAL USE OF A DRUG PRODUCT PRIOR TO THE ***46 ****2679** EXPIRATION DATE OF A PATENT CLAIMING THAT DRUG PRODUCT CONSTITUTES PATENT INFRINGEMENT, EVEN THOUGH THE ONLY PURPOSE OF THE EXPERIMENTS IS TO SEEK FDA APPROVAL FOR THE COMMERCIAL SALE OF THE DRUG AFTER THE PATENT EXPIRES. IT IS THE COMMITTEE'S VIEW THAT EXPERIMENTAL ACTIVITY DOES NOT HAVE ANY ADVERSE ECONOMIC IMPACT ON THE PATENT OWNER'S EXCLUSIVITY DURING THE LIFE OF A PATENT, BUT PREVENTION OF SUCH ACTIVITY WOULD EXTEND THE PATENT OWNER'S COMMERCIAL EXCLUSIVITY BEYOND THE PATENT EXPIRATION DATE.

ARTICLE 1, SECTION 8, CLAUSE 8 OF THE CONSTITUTION EMPOWERS CONGRESS TO GRANT EXCLUSIVE RIGHTS TO AN INVENTOR FOR A LIMITED TIME. THAT LIMITED TIME SHOULD BE A DEFINITE TIME AND, THEREAFTER, IMMEDIATE COMPETITION SHOULD BE ENCOURAGED. FOR THAT REASON, TITLE I OF THE BILL PERMITS THE FILING OF ABBREVIATED NEW DRUG APPLICATIONS BEFORE A PATENT EXPIRES AND CONTEMPLATES THAT THE EFFECTIVE APPROVAL DATE WILL BE THE EXPIRATION DATE OF THE VALID PATENT COVERING THE ORIGINAL PRODUCT. OTHER SECTIONS OF TITLE II PERMIT THE EXTENSION OF THE TERM OF A PATENT FOR A DEFINITE TIME PROVIDED CERTAIN CONDITIONS ARE MET. THERE SHOULD BE NO OTHER DIRECT OR INDIRECT METHOD OF EXTENDING PATENT TERM.

REMEDIES FOR PATENT INFRINGEMENT (SECTION 271(C)(3)-(4))

IN AN INFRINGEMENT ACTION PURSUANT TO THIS SECTION, NO INJUNCTIVE OR OTHER RELIEF COULD BE GRANTED TO PROHIBIT THE ACTIVITY WHICH IS PERMITTED BY SECTION 271(E)(1).

THE COMMITTEE EXPECTS THAT INFRINGEMENT ACTIONS PURSUANT TO THIS SECTION WILL ONLY BE BROUGHT IN THE INSTANCE DESCRIBED IN SECTION 271(E)(2), WHERE A PARTY SUBMITTING AN ABBREVIATED NEW DRUG APPLICATION UNDER TITLE I OF THIS BILL CERTIFIES THAT A PATENT IS INVALID OR NON-INFRINGED AND GIVES THE REQUIRED NOTICE OF THAT CERTIFICATION TO THE PATENT OWNER. IN THE EVENT THE PATENT IS FOUND TO BE VALID AND INFRINGED, SO THAT THE ACT OF INFRINGEMENT DESCRIBED IN SECTION 271(E)(2) HAS OCCURRED, THE REMEDIES AVAILABLE TO THE COURT ARE THREE-FOLD.

IF THE INFRINGING PARTY HAS NOT BEGUN COMMERCIAL MARKETING OF THE DRUG, INJUNCTIVE RELIEF MAY BE GRANTED TO PREVENT ANY COMMERCIAL ACTIVITY WITH THE DRUG AND THE FDA WOULD BE MANDATED TO MAKE THE EFFECTIVE DATE OF ANY APPROVED ANDA NOT EARLIER THAN THE EXPIRATION DATE OF THE INFRINGED PATENT. THE INJUNCTION COULD NOT PROHIBIT THE INFRINGING PARTY FROM USING THEIR INFORMATION CONTAINED IN THE APPLICATION TO SUPPORT THE APPROVAL OF THE APPLICATION AT THE LATER EFFECTIVE DATE. IN THE CASE WHERE THE ANDA HAD NOT BEEN APPROVED, THE ORDER WOULD MANDATE THE EFFECTIVE DATE OF ANY APPROVAL TO BE NOT EARLIER THAN THE EXPIRATION DATE OF THE INFRINGED PATENT. IN THE CASE WHERE AN ANDA HAD BEEN APPROVED, THE ORDER WOULD MANDATE A CHANGE IN THE EFFECTIVE DATE.

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IF THE INFRINGING PARTY HAS BEGUN COMMERCIAL MARKETING OF THE DRUG, DAMAGES AND OTHER MONETARY RELIEF AND INJUNCTIVE RELIEF MAY BE AWARDED FOR THE INFRINGEMENT AND TO PREVENT FURTHER INFRINGEMENT. IN ADDITION, THE FDA WOULD BE MANDATED TO CHANGE THE EFFECTIVE DATE OF THE APPROVED ANDA TO THE EXPIRATION DATE OF THE INFRINGED PATENT.

***47 **2680** SECTION 203 OF THE BILL

SECTION 203 ADDS A NEW PROVISIONS TO SECTION 282 OF TITLE 35, UNITED STATES CODE.

DEFENSES TO PATENT INFRINGEMENT (SECTION 282)

THE NEW PROVISION IN SECTION 282 PROVIDES THAT AN IMPROPER GRANT OF PATENT EXTENSION, OR ANY PORTION THEREOF, BECAUSE OF A MATERIAL FAILURE BY THE APPLICANT OR BY THE COMMISSIONER OF PATENTS AND TRADEMARKS TO COMPLY WITH THE REQUIREMENTS OF SECTION 156, IS A DEFENSE IN ANY ACTION INVOLVING THE INFRINGEMENT OF THE PATENT DURING THE PATENT EXTENSION. ANY FAILURE BY THE APPLICANT TO COMPLY WITH THE REQUIREMENTS OF SECTION 156 WOULD BE CONSIDERED MATERIAL ONLY IF THE FAILURE WOULD HAVE CHANGES THE DECISION TO GRANT THE EXTENSION OR THE LENGTH OF THE EXTENSION. ANY FAILURE BY THE COMMISSIONER TO COMPLY WITH THE REQUIREMENTS OF SECTION 156 WOULD BE CONSIDERED MATERIAL UNLESS THE COMMISSIONER FAILED TO MEET A TIME DEADLINE.

UNDER THIS PROVISION, A COURT WHICH FOUND SOME PORTION OF THE EXTENSION TO BE IMPROPERLY GRANTED WOULD NOT INVALIDATE THE ENTIRE PATENT EXTENSION. FOR EXAMPLE, IF THE COMMISSIONER MADE A MATHEMATICAL ERROR THAT RESULTED IN A FIVE YEAR EXTENSION INSTEAD OF THE FOUR YEAR EXTENSION TO WHICH THE APPLICANT WAS ENTITLED, THE COURT WOULD INVALIDATE ONLY THAT PORTION OF THE PATENT EXTENSION IMPROPERLY GRANTED.

IMPLICIT IN SECTION 156 IS A DIRECTIVE TO THE COMMISSIONER TO CORRECT ANY FAILURE ON HIS PART THAT RESULTED IN THE FUNDING OF INVALIDITY OF A PATENT EXTENSION OR ANY PORTION OF IT. THE NEW PROVISION DOES NOT CREATE ANY CAUSE OF ACTION UNDER THE TORT CLAIMS ACT AGAINST THAT COMMISSIONER OR ANY PATENTS AND TRADEMARKS OFFICE EMPLOYEE INVOLVED WITH THE EXTENSION.

IN AN ACTION INVOLVING THIS NEW PROVISION, THE DETERMINATION REGARDING DUE DILIGENCE MADE UNDER SECTION 156(D)(2) IS NOT SUBJECT TO REVIEW.

AGENCY VIEWS

AGENCY COMMENTS WERE SUBMITTED BY THE FOOD AND DRUG ADMINISTRATION DURING THE JULY 15, 1983, HEARING OF THE SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT.

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***71 **2681** MINORITY VIEWS OF MR. BLILEY

INTRODUCTION

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H.R. 3605, AS REPORTED BY THE COMMITTEE, IS A BILL DESCRIBED BY ITS PROPONENTS AS HAVING SOMETHING FOR EVERYONE-- RESTORATION OF PATENT TERMS FOR PRODUCTS SUBJECT TO ELABORATE PREMARKET APPROVAL REQUIREMENTS TO PROVIDE INCENTIVES FOR PHARMACEUTICAL RESEARCH AND FACILITATION OF APPROVAL OF GENERIC DRUGS BY THE FOOD AND DRUG ADMINISTRATION UNDER ABBREVIATED APPLICATION PROCEDURES TO INCREASE DRUG PRICE COMPETITION. THE OBJECTIVES OF THIS LEGISLATION ARE SALUTARY AND HAVE THE SUPPORT OF ALL INTERESTED PARTIES. IN MY VIEW, HOWEVER, THE LEGISLATION FAILS TO ACHIEVE A PROPER BALANCE BETWEEN THESE TWO OBJECTIVES.

INSTEAD OF PROVIDING AN APPROPRIATE PATENT TERM FOR PHARMACEUTICALS BY RESTORING THE TIME DEVOTED TO PERIODS OF 'REGULATORY REVIEW,' THE BILL STRICTLY LIMITS THE TYPES OF PATENTS ELIGIBLE FOR TERM RESTORATION AND THE CONDITIONS AND LENGTH OF THE RESTORATION PERIOD. IN SHORT, THE PATENT TERM RESTORATION PROVISIONS OF THIS BILL ARE LARGELY ILLUSORY. MOREOVER, THE BILL WOULD OVERRULE A DECISION OF THE HIGHEST PATENT COURT IN THIS COUNTRY AND THEREBY ALLOW GENERIC DRUG COMPANIES TO USE A PATENTED PRODUCT DURING THE TERM OF THE PATENT. THIS IS A SUBSTANTIAL DIMINUTION OF THE RIGHTS CURRENTLY HELD BY THE OWNER OF THE PATENT AND HAS SERIOUS CONSTITUTIONAL AND POLICY IMPLICATIONS WHICH HAVE NOT BEEN CONSIDERED BY THE COMMITTEE. THE PATENT PROVISIONS OF THIS BILL ALSO ENCOURAGE PATENT 'JUMPING' AND LITIGATION OVER THE VALIDITY OF PATENTS.

THE ABBREVIATED NEW DRUG APPLICATION (ANDA) PROVISIONS OF THIS BILL ARE EQUALLY TROUBLESOME. FOR EXAMPLE, THE BILL HAS SUBSTANTIAL ADVERSE EFFECTS ON THE RESOURCES AND LEGAL AUTHORITY OF THE FOOD AND DRUG ADMINISTRATION, WHICH HAS EXPRESSED SOME OF ITS CONCERNS ABOUT THE BILL IN A DOCUMENT ENTITLED 'TECHNICAL COMMENTS ON JUNE 2 DISCUSSION DRAFT ANDA/PATENT TERM RESTORATION LEGISLATION,' LARGELY TO NO AVAIL. MANY MEMBERS OF THE CONGRESS AND VARIOUS PRESTIGIOUS ACADEMIC AND STUDY GROUPS HAVE EXPLORED RECENTLY THE NEED FOR FASTER APPROVALS OF INNOVATIVE AND MEDICALLY NECESSARY NEW DRUGS. THE NEED TO ACCELERATE THE APPROVAL OF NEW DRUGS HAS BEEN ACKNOWLEDGED BY NEARLY EVERYONE, INCLUDING THE FDA. IT IS ASTONISHING, IN LIGHT OF THE WIDELY HELD VIEW THAT THE NEW DRUG APPROVAL PROCESS TAKES TOO LONG, THAT THE COMMITTEE REPORTED H.R. 3605, WHICH IMPOSES SUBSTANTIAL NEW ADMINISTRATIVE AND RESOURCE BURDENS ON THE FDA WHICH WILL ALMOST CERTAINLY HAVE THE EFFECT OF FORCING FDA TO DIVERT RESOURCES FROM THE REVIEW AND APPROVAL OF NEW THEREPEUTIC ENTITIES TO THE REVIEW AND APPROVAL OF COPIES OF ALREADY-AVAILABLE DRUGS.

I AM DEEPLY CONCERNED THAT IN ITS HASTE TO REPORT THIS LENGTHY AND COMPLEX BILL, THE COMMITTEE HAS FAILED TO CONSIDER FULLY AND ADEQUATELY ITS EFFECTS-- INTENDED AND UNINTENDED, DESIRABLE AND UNDESIRABLE-- IN ***72** EITHER HEARINGS OR MARKUP. H.R. 3605 IS A SIGNIFICANT PIECE OF LEGISLATION WITH IMPORTANT IMPLICATIONS FOR CONSUMERS, RESEARCH-****2682** BASED PHARMACEUTICAL COMPANIES, GENERIC DRUG COMPANIES AND FOR THE FDA. IN POINT OF FACT, HOWEVER, THE COMMITTEE HAS REPORTED A HIGHLY SIGNIFICANT AND LENGTHY BILL WITHOUT ANY HEARINGS HAVING BEEN HELD ON IT IN EITHER THE HEALTH SUBCOMMITTEE OR IN THE FULL COMMITTEE. IT IS NO ANSWER TO SAY THAT THE BILL IS THE RESULT OF LENGTHY NEGOTIATIONS BETWEEN THE BRANDNAME AND GENERIC DRUG INDUSTRY TRADE ASSOCIATIONS. MANY SIGNIFICANT INTERESTS, INCLUDING THE HIGHLY INNOVATIVE AND RESEARCH-ORIENTED PHARMACEUTICAL FIRMS HAVE SERIOUS RESERVATIONS ABOUT THE BILL AS REPORTED AS APPARENTLY, DOES THE FDA.

H.R. 3605 IS AN ADMIRABLE BEGINNING TO THE PROCESS OF STRIKING AN APPROPRIATE

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BALANCE AMONG A VARIETY OF COMPETING AND IMPORTANT POLICY OBJECTIVES. THERE IS AMPLE TIME FOR, AND A COMPELLING NEED TO, CONSIDER, REVISE AND IMPROVE UPON THE BILL. IN MY VIEW, THE BILL SHOULD BE RETURNED TO THE HEALTH SUBCOMMITTEE FOR FURTHER HEARINGS AND AMENDMENT, RATHER THAN BEING REPORTED IN HASTE BY THIS COMMITTEE. FURTHER, BECAUSE THIS COMMITTEE LACKS EXPERTISE IN PATENT MATTERS, THE COMMITTEE IS NOT QUALIFIED TO EVALUATE THE PATENT PROVISIONS OF H.R. 3605. WE DO THIS INSTITUTION A DISSERVICE BY HASTILY REPORTING ON THE VERY DAY OF INTRODUCTION, A COMPLEX BILL OUTSIDE THE EXPERTISE OF THE COMMITTEE AFTER A 'MARKUP' THAT LASTED BARELY THIRTY MINUTES.

IN THE NEXT SECTIONS OF MY VIEWS, I DESCRIBE IN GREATER DETAIL THE SIGNIFICANT AREAS IN WHICH THIS BILL IS DEFICIENT.

I. TITLE I-- ABBREVIATED NEW DRUG APPLICATIONS

A. LIMITS ON FDA AUTHORITY

BOTH THE RESEARCH-BASED PHARMACEUTICAL COMPANIES WHICH FAVOR AMENDMENTS TO H.R. 3605 AND THE FDA ITSELF HAVE IDENTIFIED WAYS IN WHICH THE BILL UNWISELY RESTRICTS FDA'S AUTHORITY TO ENSURE THAT ALL DRUGS ARE DEMONSTRATED TO BE SAFE AND EFFECTIVE.

FIRST, THE BILL EXPRESSLY PROHIBITS FDA FROM REQUESTING DATA ON THE SAFETY OR EFFICACY OF CERTAIN GENERIC DRUGS, EVEN WHERE SUCH DATA ARE NEEDED TO FULFILL THE FDA'S PUBLIC HEALTH RESPONSIBILITIES. ALTHOUGH ONE WOULD NOT ANTICIPATE THAT FDA WOULD NEED TO RESORT TO THIS AUTHORITY VERY OFTEN, I BELIEVE IT IS A FUNDAMENTAL MISTAKE TO DEPRIVE THE FDA OF THE AUTHORITY SIMPLY BECAUSE IT IS ASSUMED THAT IT WILL NEED TO EXERCISE IT ONLY RARELY.

SECOND, IT HAS BEEN THE LONGSTANDING POLICY OF FDA TO REQUIRE THAT PERSONS SEEKING TO MARKET DRUGS COMBINING TWO OR MORE ACTIVE INGREDIENTS DEMONSTRATE THAT THE COMBINATION ITSELF, AS OPPOSED TO THE ACTIVE INGREDIENTS INDIVIDUALLY, BE SHOWN TO BE SAFE AND EFFECTIVE. FDA'S AUTHORITY TO REQUIRE THIS PROOF HAS BEEN UPHELD BY THE COURTS. WITHOUT EXPLANATION OR HEARING, H.R. 3605 WOULD OVERRULE THIS POLICY AND LIMIT FDA'S CONSIDERATION OF SAFETY AND EFFICACY TO THE INDIVIDUAL ACTIVE INGREDIENTS OF COMBINATION DRUGS. I DO NOT BELIEVE THAT THE CONGRESS SHOULD PROVIDE FOR THE APPROVAL OF NEW COMBINATIONS OF DRUGS WITHOUT REQUIRING THE APPLICANT TO DEMONSTRATE THAT THE COMBINATION IS SAFE AND EFFECTIVE. THE PUBLIC HEALTH SHOULD NOT BE COMPROMISED IN THIS FASHION.

***73 **2683** B. RESOURCE IMPLICATIONS

THE REVIEW AND APPROVAL BY FDA OF NEW PHARMACEUTICALS-- OFTEN INNOVATIVE AND HIGHLY DESIRABLE DEVELOPMENTS ESSENTIAL TO THE HEALTH OF OUR CITIZENS-- IS PERHAPS THE MOST IMPORTANT FUNCTION THAT THE CONGRESS HAS GIVEN TO THE FDA. THE AMERICAN PEOPLE AND THE MEMBERS OF THE CONGRESS RIGHTLY EXPECT THAT THIS FUNCTION BE PERFORMED COMPETENTLY AND EXPEDITIOUSLY. NEW DRUGS ARE OFTEN INEXPENSIVE WAYS TO CURE LIFE-THREATENING OR DEBILITATING DISEASES. UNNECESSARY DELAY IN MAKING THESE DRUGS AVAILABLE TO PHYSICIANS HAS BEEN A CONTINUING CONCERN TO ME, MANY OTHER MEMBERS OF THE CONGRESS, TO THE FDA, TO THE MEDICAL COMMUNITY AND OTHERS. THE

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SO-CALLED 'DRUG LAG' AND THE NEED TO EXPEDITE DRUG APPROVALS HAS BEEN WIDELY STUDIED AND RECOMMENDATIONS FOR IMPROVEMENTS ABOUND. INDEED, FDA IS IN THE MIDST OF REVISING ITS REGULATIONS AND PROCEDURES FOR NEW DRUG APPROVALS.

ASTONISHINGLY, THEN, THE COMMITTEE HAS REPORTED A BILL WHICH IS LIKELY TO REDUCE FDA'S ABILITY TO IMPROVE ITS NEW DRUG APPROVAL PROCEDURES AND ITS TIMELINESS IN ACTING ON NEW DRUG APPLICATIONS. FDA HAS EXPRESSED CONCERN IN ITS 'TECHNICAL COMMENTS' THAT THE BILL REPORTED BY THE COMMITTEE WILL RESULT IN A 'SUBSTANTIAL INCREASE IN WORK LOAD DURING THE FIRST FEW YEARS IMMEDIATELY FOLLOWING ENACTMENT.' IT IS OBVIOUS THAT THIS INCREASE IN WORKLOAD WILL OBLIGATE FDA TO REALLOCATE PERSONNEL FROM NEW DRUG REVIEW TO ANDA REVIEW. BECAUSE THE BILL ALSO CONTAINS TIME LIMITS ON FDA'S ACTIONS ON ANDAS WHICH ARE FAR MORE RESTRICTIVE THAN THOSE FOR NDAS, [FN21] THIS PROBLEM WILL BE FURTHER EXACERBATED. IT IS APPARENTLY THE COMMITTEE'S VIEW THAT REVIEW OF ANDAS IS A MORE IMPORTANT PRIORITY FOR FDA THAN NDAS. I TAKE STRONG EXCEPTION TO THAT JUDGMENT.

AS FDA HAS SUGGESTED, A PHASE-IN OF ELIGIBILITY OF ANDAS WOULD AMELIORATE MUCH OF ITS WORKLOAD BURDEN WHILE SIMULTANEOUSLY MAKING AVAILABLE IMMEDIATELY FOR ANDA TREATMENT SIX OF THE DRUGS THAT ARE AMONG THE TOP SELLING PRESCRIPTION DRUG PRODUCTS. I URGE THE MEMBERS OF THE HOUSE TO CONSIDER THIS IDEA AMONG OTHERS AS A WAY TO GREATLY IMPROVE UPON THIS BILL.

C. DISCLOSURE OF PROPRIETARY DATA

THE BILL REPORTED BY THE COMMITTEE PROVIDES FOR THE PUBLIC DISCLOSURE OF ALL OF THE EXTENSIVE AND COSTLY RESEARCH DATA GENERATED BY RESEARCH-ORIENTED PHARMACEUTICAL COMPANIES, EVEN THOUGH THOSE SAFETY AND EFFECTIVENESS DATA MAY BE OF SIGNIFICANT VALUE TO FOREIGN COMPETITORS OR MAY RETAIN PROPRIETARY VALUE IN THE UNITED STATES. THESE DATA MAY WELL RETAIN COMMERCIAL VALUE, EVEN WHEN FDA NO LONGER REQUIRES AN APPLICANT TO SUBMIT THEM FOR APPROVAL OF A DRUG (I.E., WHEN AN ANDA MAY BE FILED WITH FDA, THE FULL DATA ARE NOT NEEDED). THE DATA MAY STILL BE VALUABLE, FOR EXAMPLE, BECAUSE IN MANY FOREIGN COUNTRIES ALL OR A PORTION OF THESE DATA ARE NEEDED TO OBTAIN APPROVAL. THESE DATA WILL BE VALUABLE PARTICULARLY IN THOSE COUNTRIES WHICH DO NOT RECOGNIZE U.S. PATENTS. BY PROVIDING FOR THE ***74 ****2684** RELEASE OF THESE DATA, THE BILL HANDS TO FOREIGN COMPETITORS OF U.S. DRUG FIRMS, FOR THE MERE PRICE OF PHOTOCOPYING CHARGES, DATA WHICH COST MANY MILLIONS OF DOLLARS TO OBTAIN AND WHICH CAN BE USED TO OBTAIN APPROVAL TO MARKET DRUGS IN COMPETITION WITH THE OWNER AND GENERATOR OF THE DATA. THIS PROVISION OF H.R. 3605 IS HARDLY THE WAY TO PROTECT AND IMPROVE THE COMPETITIVENESS OF AMERICA'S PHARMACEUTICAL INDUSTRY.

IT SHOULD ALSO BE NOTED THAT THIS PROVISION OF H.R. 3605 HAS SIGNIFICANT RESOURCE IMPLICATIONS FOR FDA. UNDER THE FREEDOM OF INFORMATION ACT, FDA IS OBLIGATED TO RESPOND TO REQUESTS FOR DOCUMENTS IN ITS FILES, INCLUDING THE VOLUMINOUS SAFETY AND EFFECTIVENESS DATA MADE AVAILABLE BY THE BILL, ORDINARILY WITHIN TEN DAYS. SINCE THE ENACTMENT OF THE FOI ACT, FDA HAS CONSISTENTLY RECEIVED MORE REQUESTS FOR DOCUMENTS THAN VIRTUALLY ANY OTHER FEDERAL AGENCY. IN 1983, FDA RECEIVED OVER 39,000 FOI REQUESTS. ONE HUNDRED TWENTY-FIVE 'FULL TIME EQUIVALENTS,' MANY HIGHLY TRAINED SCIENTISTS AND DOCTORS, WERE REQUIRED TO PROCESS THESE REQUESTS. UNDER H.R. 3605, OVER TWENTY YEARS OF SAFETY AND EFFECTIVENESS

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DATA AND INFORMATION WILL, IMMEDIATELY UPON ENACTMENT, BE AVAILABLE FOR DISCLOSURE. IF FDA WERE TO RECEIVE REQUESTS FOR EVEN A MODEST PART OF THOSE DATA, THE WORKLOAD AND RESOURCE BURDENS WOULD BE STAGGERING. I FAIL TO SEE HOW THE PUBLIC BENEFITS BY HAVING FDA BE FORCED TO DIVERT SCARCE TECHNICAL PERSONNEL AND RESOURCES TO PROCESSING FDA REQUESTS AND ANDAS, AT THE EXPENSE OF NEW DRUG APPLICATIONS AND OTHER IMPORTANT PUBLIC HEALTH FUNCTIONS.

II. TITLE II-- PATENT TERM RESTORATION

H.R. 3605 CONTAINS MANY SIGNIFICANT REVISIONS TO OUR PATENT LAWS. RATHER THAN RESTORING PATENT TERMS LOST DURING EXTENSIVE REGULATORY REVIEW PERIODS, THESE REVISIONS ELIMINATE MANY OF THE SIGNIFICANT RIGHTS WHICH CURRENTLY ACCRUE TO THE PATENT OWNER. MOREOVER, THE PATENT TERM RESTORATION PROVISIONS ARE SO RESTRICTIVE THAT THEIR EFFECT MAY WELL BE LARGELY ILLUSORY. INNOVATION IS NOT ENCOURAGED BY THESE PATENT PROVISIONS.

A. LOSS OF PATENT RIGHTS

I AM ADVISED THAT IT HAS LONG BEEN ACCEPTED THAT TO USE, SELL OR MAKE A PATENTED PRODUCT DURING THE LIFE OF THE PATENT CONSTITUTES PATENT INFRINGEMENT. THIS ASPECT OF THE RIGHTS ACCRUING TO THE PATENT OWNER WAS RECENTLY REAFFIRMED IN THE CONTEXT OF GENERIC DRUGS IN THE SO-CALLED BOLAR CASE. THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT HELD, CONSISTENT WITH PRIOR LAW, THAT A GENERIC DRUG COMPANY MAY NOT FORMULATE AND TEST ITS VERSION OF ANOTHER COMPANY'S PATENTED DRUG UNTIL THE PATENT TERM EXPIRES. THE BOLAR DECISION IS SOUND LAW AND SHOULD BE RETAINED.

H.R. 3605, HOWEVER, WOULD OVERRULE BOLAR AND THEREBY PERMIT A GENERIC DRUG COMPANY TO ENGAGE IN ACTS WHICH HERETOFORE WOULD HAVE CONSTITUTED PATENT INFRINGEMENT. IT IS EXTREMELY DOUBTFUL THAT IT IS SOUND POLICY IN A BILL DESIGNED TO RESTORE PATENT LIFE, TO DRAMATICALLY CUT BACK ON EXISTING PATENT RIGHTS.

I AM ALSO CONCERNED THAT THE CONSTITUTIONAL IMPLICATIONS OF THIS PROVISION OF H.R. 3605 HAVE NOT BEEN CONSIDERED. BY OVERRULING BOLAR, THE BILL RETROSPECTIVELY DEPRIVES THE PATENT HOLDER OF VALUABLE ***75 **2685** RIGHTS. PATENT RIGHTS REPRESENT BOTH A CONTRACTUAL RIGHT BETWEEN THE PATENT HOLDER AND THE U.S. GOVERNMENT AND A RECOGNIZED PROPERTY RIGHT. THE CONSTITUTION PREVENTS THE GOVERNMENT FROM IMPAIRING THE RIGHTS OF CONTRACT AND FROM 'TAKING' OR DEPRIVING ONE OF A PROPERTY RIGHT WITHOUT JUST COMPENSATION. BY OVERRULING BOLAR FOR PATENTS ALREADY ISSUED, H.R. 3605 VIOLATES THESE IMPORTANT PROTECTIONS FOUND IN OUR CONSTITUTION.

B. RESTRICTIONS ON PATENT TERM RESTORATION

UNDER H.R. 3605, MOST PATENTS WILL NOT BE ELIGIBLE FOR RESTORATION, EVEN THOUGH THEY MAY COVER PRODUCTS OR METHODS OF USE, FORMULATION OR ADMINISTRATION, OF INNOVATIVE DRUGS WHICH REQUIRED MANY YEARS AND GREAT EXPENSE TO RESEARCH AND DEVELOP AND EVEN THOUGH MANY YEARS MAY HAVE BEEN DEVOTED TO SECURING AN APPROVAL TO MARKET FROM THE FDA. THE BILL THUS FAILS TO ACHIEVE ONE OF ITS PRINCIPAL PURPOSES: TO ENSURE THAT SUFFICIENT INCENTIVES EXIST FOR INNOVATION.

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A FEW EXAMPLES OF THE RESTRICTIVE APPROACH TO PATENT TERM RESTORATION WILL DEMONSTRATE THE INADEQUACIES OF H.R. 3605.

UNDER PRESENT LAW, A PATENT CAN BE OBTAINED CONTAINING A BROAD CLAIM (GENUS) COVERING MANY COMPOUNDS. IT IS DIFFICULT AND REQUIRES A LARGE INVESTMENT BY THE INNOVATOR, BUT IS STILL POSSIBLE SUBSEQUENTLY TO OBTAIN A PATENT FOR SPECIFIC CLAIMS (SPECIES) ON A FEW SPECIFIC COMPOUNDS ENCOMPASSED WITHIN THE GENUS. UNDER THE BILL, SHOULD A PATENT HOLDER OBTAIN A PATENT WITH SPECIES CLAIMS COVERED BY A PREVIOUSLY-ISSUED GENUS PATENT, THE PATENT HOLDER COULD NOT OBTAIN RESTORATION OF THE TERM OF THE SPECIES PATENT.

IN ADDITION, UNDER PRESENT LAW, THE PATENT OFFICE CAN REQUIRE THAT THE CLAIMS IN A PATENT APPLICATION BE DIVIDED AND PROSECUTED IN SEPARATE PATENTS. UNDER THE BILL, THE FIRST ISSUED PATENT OF THE SERIES WOULD BE THE ONLY PATENT TERM ENTITLED TO RESTORATION, AND SUBSEQUENTLY ISSUED PATENTS OF THE SERIES WOULD BE PRECLUDED FROM RESTORATION. ACCORDINGLY, UNLESS AN FDA APPROVED PRODUCT IS CLAIMED WITHIN THE FIRST ISSUED PATENT OF THE SERIES, RESTORATION OF A PATENT TERM COVERING THE PRODUCT WOULD NOT BE AVAILABLE. DURING THE PATENT APPLICATION PROCESS, IT IS IMPOSSIBLE TO KNOW WHICH DRUG OR DRUGS WILL ULTIMATELY BE SUCCESSFULLY TESTED AND MARKETED. THEREFORE, A PATENT HOLDER IS BEING DENIED THE BENEFIT OF PATENT TERM RESTORATION DUE TO CIRCUMSTANCES BEYOND ITS CONTROL.

ANOTHER EXCEPTION TO PATENT TERM RESTORATION ENCOMPASSED BY H.R. 3605 WOULD OCCUR WHERE ONE PATENT COVERS TWO FDA APPROVED DRUGS. ANY CLAIMS IN THE PATENT COVERING THE SECOND FDA APPROVED DRUG COULD NOT BE RESTORED. ACCORDINGLY, ONLY ONE RESTORATION IS AVAILABLE PER PATENT EVEN THOUGH A COMPANY MAY HAVE EXPENDED CONSIDERABLE RESOURCES IN DEVELOPING EACH FDA APPROVED PRODUCT.

THE BILL ALSO LIMITS AVAILABILITY OF PATENT TERM RESTORATION FOR METHOD OF MANUFACTURING PATENTS (NOT USING DNA TECHNOLOGY), INCLUDING THE LIMITATION THAT NO OTHER TYPE OF PATENT HAS BEEN OR 'MAY BE ISSUED FOR ANY KNOWN THERAPEUTIC PURPOSES' CLAIMING THE METHOD OF USING THE PRODUCT.

BY EXCLUDING SO MANY PATENTS FROM ELIGIBILITY FOR TERM RESTORATION AND BY MAKING THE ELIGIBILITY FOR RESTORATION OF SOME PATENTS TURN ON CIRCUMSTANCES BEYOND THE CONTROL OF THE INNOVATOR, THE BILL FALLS WELL SHORT OF PROVIDING THE INCENTIVES FOR INNOVATION THAT IT ***76 **2686** PURPORTS TO ACHIEVE. IT IS NOT NECESSARY, OR COURSE, THAT EVERY PATENT BE ELIGIBLE FOR EXTENSION IN ORDER FOR REASONABLE INCENTIVES TO INNOVATE TO EXIST. RATHER, THE BILL SHOULD PROVIDE FOR PATENT TERM RESTORATION FOR ALL SIGNIFICANT INNOVATIONS, BE THEY IN DISCOVERING NEW CHEMICAL ENTITIES, NEW DOSAGE FORMS, NEW USES OR SPECIES OF SUBSTANCES PREVIOUSLY COVERED BY BROAD GENUS PATENTS. THE RESTRICTIVE ELIGIBILITY PROVISIONS OF H.R. 3605 MAKE PATENT TERM RESTORATION A HAPHAZARD AND INFREQUENT EVENT. INNOVATION IS NOT ENCOURAGED WHEN THE PROSPECT OF MEANINGFUL PATENT LIFE IS LEFT TO CHANCE AND HAPPENSTANCE AND WHEN MOST INNOVATIONS COVERED BY PATENTS WILL NOT BE ELIGIBLE FOR TERM RESTORATION.

H.R. 3605 ALSO MAKES OTHER SIGNIFICANT CHANGES TO OUR PATENT LAWS WHICH NEITHER I NOR THIS COMMITTEE HAVE HAD TIME TO LEARN ABOUT OR CONSIDER.

III. CONCLUSION

IT IS DISTRESSING AND REGRETTABLE THAT THIS COMMITTEE HAS REPORTED A COMPLEX,

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LENGTHY AND HIGHLY SIGNIFICANT PIECE OF LEGISLATION WITHOUT HOLDING HEARINGS IN EITHER THE HEALTH SUBCOMMITTEE OR IN THE FULL COMMITTEE AND AFTER WHAT CAN ONLY BE DESCRIBED AS A PRO FORMA MARKUP. IT IS EQUALLY DISTRESSING THAT THIS COMMITTEE REPORTED A CONTROVERSIAL BILL WHICH CHANGES SIGNIFICANTLY OUR PATENT LAWS, AN AREA WHICH ESCAPES EVEN THE BROAD JURISDICTION OF THIS COMMITTEE.

I SHARE WITH OTHER MEMBERS THE DESIRE TO RESTORE PATENT LIFE LOST DURING PERIODS OF REGULATORY REVIEW AND THE DESIRE TO FACILITATE THE APPROVAL OF GENERIC DRUGS. I OBJECT, HOWEVER, TO THE PRECIPITOUS AND SUPERFICIAL CONSIDERATION OF THE BILL BY THE COMMITTEE AND TO ITS FAILURE TO PROVIDE FOR AND CONSIDER, THE VIEWS OF ALL PARTIES AFFECTED BY THE LEGISLATION.

THOMAS J. BLILEY, JR.

FN1 21 U.S.C. 355.

FN2 THE TERM 'LISTED DRUG' IS EXPLAINED IN PARAGRAPH (6) OF NEW SECTION 505(J) OF THE FFDCA. GENERALLY, A LISTED DRUG INCLUDES ANY DRUG THAT HAS BEEN APPROVED FOR SAFETY AND EFFECTIVENESS OR THAT HAS BEEN APPROVED UNDER NEW SUBSECTION (J).

FN3 48 FED.REG. 2751(1983).

FN4 ID. AT 2753.

FN5 ID. AT 2755. 21 C.F.R. 314.2(C) PROVIDES IN PART: 'A PROSPECTIVE APPLICANT MAY SEEK A DETERMINATION OF THE SUITABILITY OF AN ABBREVIATED NEW DRUG APPLICATION FOR A PRODUCT THAT THE APPLICANT BELIEVES SIMILAR OR RELATED TO A DRUG PRODUCT THAT HAS BEEN DECLARED TO BE SUITABLE FOR AN ABBREVIATED NEW DRUG APPLICATION . . . '

FN6 ID. AT 2756. SEE 21 CFR 314.2(F)(4), (5), (6), (7), AND (8).

FN7 ID. AT 2755. SEE 21 CFR 314.2(C).

FN8 ID. AT 2752.

FN9 ID.

FN10 21 U.S.C. 321(P). FOR EXAMPLE, A DRUG MARKETED PRIOR TO 1938 AND UNCHANGED IS A 'GRANDFATHERED DRUG' AND THUS NOT WITHIN THE SCOPE OF THE DEFINITION OF 'NEW DRUG' SET FORTH IN SECTION 201(P) OF THE FFDCA. ANOTHER EXAMPLE OF A DRUG OUTSIDE THE SCOPE OF SECTION 201(P) IS A PRODUCT THAT IS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND THAT HAS BEEN USED TO A MATERIAL EXTENT OR FOR A MATERIAL TIME.

FN11 21 U.S.C. 352(E)(1)-(4).

FN12 SEE UNTRUE STATEMENTS IN APPLICATION, 21 C.F.R. 314.12(1982).

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FN13 THE COMMITTEE RECOGNIZES THAT, IN CERTAIN INSTANCES, THE PATENT OWNER MAY AGREE WITH THE CERTIFICATION OF THE APPLICANT. FOR EXAMPLE, WHEN THE APPLICANT CERTIFIES THAT PATENT NO. 1 IS INVALID AND PATENT NO. 2 IS NOT INFRINGED, THE PATENT OWNER MAY AGREE WITH THE CERTIFICATION REGARDING PATENT NO. 2. THEN AN ACTION FOR PATENT INFRINGEMENT NEED ONLY BE BROUGHT WITH RESPECT TO PATENT NO. 1.

FN14 28 U.S.C. 1407.

FN15 SEE DEFINITION OF BIOAVAILABILITY, 21 C.F.R. 320.1(A)(1982).

FN16 SEE DEFINITION OF BIOEQUIVALENT DRUG PRODUCTS, 21 C.F.R. 320.1(E)(1982).

FN17 THE COMMITTEE RECOGNIZES THAT IN CERTAIN INSTANCES, THE PATENT OWNER MAY AGREE WITH THE CERTIFICATION OF THE APPLICANT. FOR EXAMPLE, WHEN THE APPLICANT CERTIFIES THAT PATENT NO. 1 IS INVALID AND PATENT NO. 2 IS NOT INFRINGED, THE PATENT OWNER MAY AGREE WITH THE CERTIFICATION REGARDING PATENT NO. 2. THEN AN ACTION FOR PATENT INFRINGEMENT NEED ONLY BE BROUGHT WITH RESPECT TO PATENT NO. 1.

FN18 SEE CONFIDENTIALITY OF DATA AND INFORMATION IN A NEW DRUG APPLICATION (NDA) FILE, 21 C.F.R. 314.14(F)(1)-(4)(1982).

FN19 21 C.F.R. 314.14(F)(5) PROVIDES: '(5) A FINAL DETERMINATION HAS BEEN MADE THAT THE DRUG MAY BE MARKETED WITHOUT SUBMISSION OF SUCH SAFETY AND/OR EFFECTIVENESS DATA AND INFORMATION.' THE COMMITTEE WAS CONCERNED THAT THIS PROVISION OF THE REGULATION MIGHT BE INTERPRETED AS PERMITTING THE DISCLOSURE OF SUCH INFORMATION AND DATA UPON ENACTMENT OF THIS BILL. THIS IS BECAUSE ALL DRUGS APPROVED FOR SAFETY AND EFFECTIVENESS PRIOR TO ENACTMENT OF THIS BILL ARE DEEMED LISTED AND THUS ELIGIBLE FOR CONSIDERATION IN AN ANDA UPON ENACTMENT OF THE BILL. THE COMMITTEE WISHED TO AVOID ANY POSSIBILITY THAT LISTING OF A DRUG UNDER THIS BILL WOULD BE DEEMED A FINAL DETERMINATION THAT THE DRUG COULD BE APPROVED WITHOUT THE SUBMISSION OF SAFETY AND EFFECTIVENESS INFORMATION.

FN20 THE PHRASE 'IDENTICALLY DISCLOSED OR DESCRIBED' IS USED IN 35 U.S.C. 103 TO SET FORTH THE CONDITIONS OF 35 U.S.C. 102.

FN21 UNDER CURRENT LAW, THE 180-DAY TIME PERIOD FOR ACTING ON AN NDA DOES NOT BEGIN UNTIL THE NDA IS 'FILED,' I.E., IS NEARLY READY TO BE APPROVED BY FDA. UNDER H.R. 3605 THE 180-DAY TIME PERIOD FOR ACTING ON AN ANDA BEGINS WHEN THE ANDA IS SUBMITTED. A SUBSTANTIAL TIME MAY PASS BETWEEN 'SUBMISSION' AND 'FILING' WHILE THE APPLICATION IS BROUGHT INTO CONFORMITY WITH FDA'S CRITERIA FOR APPROVAL.

(Note: 1. PORTIONS OF THE SENATE, HOUSE AND CONFERENCE REPORTS, WHICH ARE DUPLICATIVE OR ARE DEEMED TO BE UNNECESSARY TO THE INTERPRETATION OF THE LAWS, ARE OMITTED. OMITTED MATERIAL IS INDICATED BY FIVE ASTERISKS: *****.
2. TO RETRIEVE REPORTS ON A PUBLIC LAW, RUN A TOPIC FIELD SEARCH USING THE PUBLIC LAW NUMBER, e.g., TO(99-495))

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